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Catalytic Enantioselective Desymmetrization of *meso*-Epoxides

Katalytická Enantioselektívna desymetrizace *meso*-Epoxidov

Diploma thesis

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Prague, 2020

Prohlášení

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V Praze, 13.08.2020 Štefan Malatinec

Abstract

Catalytic enantioselective desymmetrization of *meso*-epoxides is widely used in many areas of chemistry. Such process is usually catalyzed by a transition metal complex with a chiral ligand. Recently, a synthesis of an analogue of Bolm's 2,2'-bipyridine ligand was developed and its combination with metal salts were tested in various reactions. In this master's thesis, a catalytic system composed of $Sc(OTf)_3$/Bolm's ligand analogue was studied in alcoholysis and aminolysis of the *meso*-epoxides. The reaction has been extended to a broad range of alcohols providing 1,2-diol monoethers in excellent enantioselectivity up to 99% ee. The aminolysis of *meso*-epoxides has been optimized, as well. The catalyst loading could be lowered to 1 mol% with only marginal effects on the enantioselectivity.

Key words: *epoxides, enantioselective catalysis, chiral ligands*.

Abstrakt

Katalytická enantioselektivní desymetrizace *meso*-epoxidů je široce používána v mnoha oblastech chemie. Takový proces je obvykle katalyzován komplexem přechodného kovu s chirálním ligandem. Nedávno byla vyvinuta syntéza analogu Bolmova 2,2'-bipyridinového ligandu a kombinace tohoto ligandu se solemi přechodných kovů byly testovány jako katalyzátory v různých reakcích. V této diplomové práci byl studován katalytický systém složený ze $Sc(OTf)_3$/analoga Bolmova ligandu při alkoholýze a aminolýze *meso*-epoxidů. Reakce byla rozšířena na širokou škálu alkoholů poskytujících 1,2-diolové monoethery ve vynikající enantioselektivitě až do 99% ee. Také byla optimalizována aminolýza meso-epoxidů. Navážka katalyzátoru mohla být snížena na 1 mol% s pouze okrajovými účinky na enantioselektivitu.

Klíčová slova: *epoxidy, enantioselektivní katalýza, chirální ligandy*.

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List of used Abbreviations

Ac	acetyl
acac	acetylacetone
BINOL	1,1'-Bi-2-naphthol
Bn	benzyl
Bpy	2,2'-bypiridine
br s	broad siglet
Bu	butyl
δ	chemical shift
DEAD	diethyl azodicarboxylate
DME	dimethoxyethane
DS	dodecylsulphate
EDTA	ethylenediaminetetraacetic acid
Et	ethyl
eq.	equivalent
Fmoc	fluorenylmethyloxycarbonyl
h	hours
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
IR	infrared spectroscopy
i-Pr	*iso*-propyl
J	coupling constant
LA	Lewis acid
Me	methyl
MS	molecular sieves
ND	not determined
Nu	nucleophile
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	per parts million
Pr	propyl
R_F	retardation factor
RT	room temperature

TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBME	*tert*-butylmethyl ether
t-Bu	*tert*-butyl
Tf	triflate
THF	tetrahydrofuran
TLC	thin liquid chromatography
Ts	tosylate

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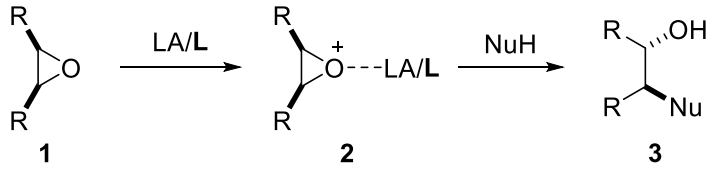
1. Introduction

Epoxides are three-membered heterocyclic molecules, which are considered to be an important class of chemicals. Their importance originates from the high reactivity of the three-membered cycle due to its inherent strain. There is a large driving force for the ring to break open and the ideal tetrahedral angles to be restored for every atom. Therefore, epoxides can be utilized as intermediates in numerous syntheses.[1]

Desymmetrization is a transformation of a prochiral *meso*-compound into a chiral one. The advantage of desymmetrization is that a number of stereogenic centers can be unveiled in a single organic transformation. This process is sometimes referred to as the '*meso*-trick' and it has found a large interest among synthetic chemists.[2] There are two types of reactions of *meso*-epoxides. One is β-deprotonation to provide chiral allyl alcohols and the other is enantioselective desymmetrization with nucleophiles to give chiral *trans*-2-substituted alcohols. Hence, many 1,2-difunctionalized organic compounds have been prepared *via* enantioselective desymmetrization of *meso*-epoxides.[3]

The typical scenario of the desymmetrization is as follows (Scheme 1). The process of the ring-opening of *meso*-epoxides **1** is usually catalyzed by a Lewis acid (LA) coordinated with a chiral ligand.[3–7] The Lewis acid activates the epoxide through its coordination to the oxygen forming intermediate **2**. This leads to a weakening of the carbon-oxygen bond which is followed by a nucleophilic attack. The role of the chiral ligand **L** is directing the nucleophilic attack to one side of the epoxide. The other side is made inaccessible by a bulky group present in the chiral ligand **L**. In other words, the nucleophile would hit the chiral fence. In this manner, the chiral ligand **L** may induce the enantioselectivity of the reaction.

Scheme 1: Scenario for enantioselective desymmetrization process.



1 **2** **3**

The following section focuses on representative synthetically useful methods of desymmetrization of *meso*-epoxides. The list of all mentioned *meso*-epoxides is placed in the Appendix for reference.

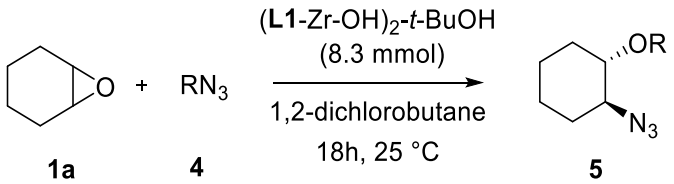
2. Theoretical Part

2.1. Ring-opening of epoxides with nitrogen nucleophiles

2.1.1. Ring-opening of epoxides with azides

Azidolysis of aliphatic *meso*-epoxides was first reported by Nugent *et al.* by using a chiral Zr-based catalyst prepared by a reaction of zirconium *tert*-butoxide in THF with alkanolamine **L1**.[8] The reaction was tested in reactions of cyclohexene oxide **1a** with azide **4a** in the presence of different additives (Table 1). The presence of an additive turned out to have a dramatic effect on the enantiomeric induction. The reaction conducted without the presence of an additive gave only poor enantioselectivity (Entry 1). The enantiomeric excess of the product increased to 70% when acetic acid was used (Entry 2). Further increase to 86% was obtained by the addition of trimethylsilyl trifluoroacetate (Entry 3) or trifluoroacetic acid to 87% (Entry 4). It was also found that enantioselectivity could be improved to 93% by lowering the reaction temperature to 0 °C and running the reaction with azide **4b** (Entry 5). In addition, different *meso*-epoxides **1** reacted with azide **4b** giving products **5** with good enantioselectivities up to 93% ee (Scheme 2).

Table 1: Azidolysis of cyclohexene epoxide **1a**.

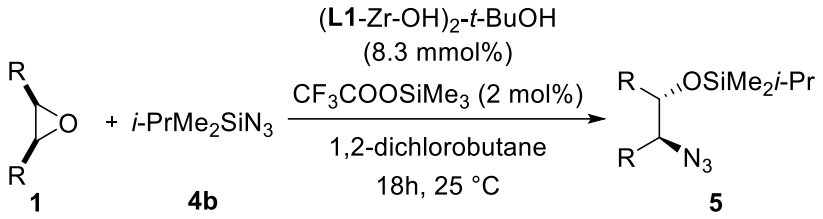


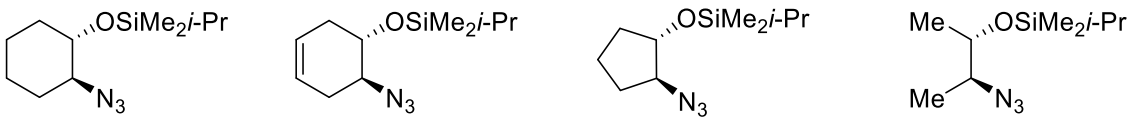
1a **4** **5**

Entry	Azide **4**	R	Additive (mol%)	ee (%)
1	**4a**	Me_3Si	-	19
2	**4a**	Me_3Si	AcOH (0.7)	70
3	**4a**	Me_3Si	$CF_3COOSiMe_3$ (1.5)	86
4	**4a**	Me_3Si	CF_3COOH (0.5)	87
5[a]	**4b**	*i*-$PrMe_2Si$	$CF_3COOSiMe_3$ (2)	93

[a] Reaction carried out at 0 °C. For ligand **L1** see Figure 1.

Scheme 2: Azidolysis of epoxides **1** with azide **4b**.

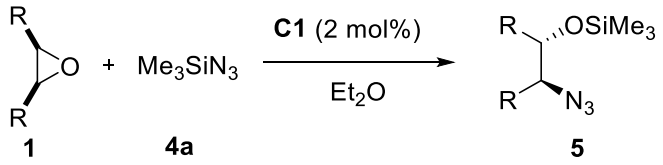


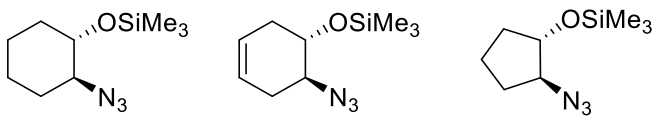


5a, 86%, 93% ee **5b**, 79%, 89% ee **5c**, 64%, 83% ee **5d**, 59%, 87% ee

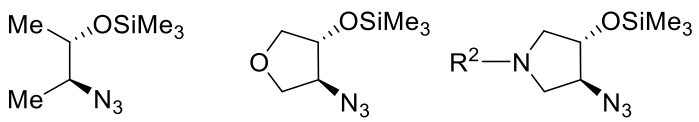
Jacobsen *et al.* studied a similar reaction as well.[9] However, the highly effective chromium(III)(salen) complex **C1** (Figure 1) was used as the catalyst. Thus, the ring-opening of various epoxides **1** with azide **4a** catalyzed by **C1** yielded 1,2-azide alcohols **5** with high enantioselectivities up to 98% (Scheme 3). Surprisingly, when aluminium, titanium or manganese complexes were used instead of the chromium one, products **5** were formed in racemic mixtures. Azidolysis catalyzed by a chromium salen complex was also performed in ionic liquids.[10]

Scheme 3: Azidolysis of epoxides **1** with azide **4a**.





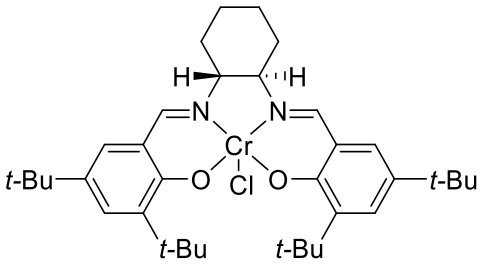
5a, 80%, 88% ee **5b**, 72%, 81% ee **5c**, 80%, 94% ee



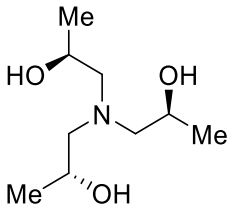
5d, 65%, 82% ee **5e**, 80%, 98% ee

5f, R^2 = Fmoc
80%, 95% ee
5g, R^2 = $COCF_3$
90%, 95% ee

Figure 1: List of catalyst and ligand mentioned in the section 2.1.1.



C1



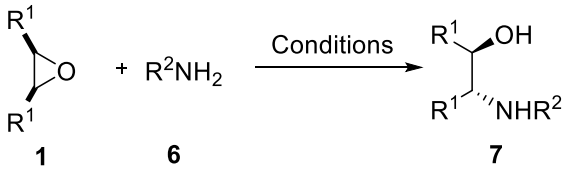
L1

2.1.2. Ring-opening of epoxides with amines

While performing the ring-opening of *meso*-epoxides with amines, one has to consider a possible competing coordination of the amines to a chiral Lewis acid catalyst with the resulting difficult activation of the epoxide. Therefore, for realizing this reaction one has to consider a suitable choice of Lewis acid, which preferentially interacts with the epoxide over the amine. Despite of this problem several groups have published works concerning ring-opening of epoxides with amines. The attractivness for making β-amino alcohols is their potential use as building blocks in syntheses of natural and bioactive compounds.[11,12] Thus, development of catalytic systems is desirable.

Initial studies of ring-opening of *meso*-epoxides with amines were conducted using two catalytic complexes containing the BINOL ligand **L2** (Figure 3). Hou *et al.* accomplished aminolysis of epoxides **1** in the presence of ytterbium(III) triflate[13] and Shibasaki *et al.* with $Pr(O\text{-}i\text{-}Pr)_3$[14]. The reactions proceeded smoothly and gave rise to β-amino alcohols **7** (Table 2). However, only poor to moderate enantioselectivities were observed (12-80% ee). Interestingly, a higher enantioselectivity was obtained in the reaction of cyclohexene oxide **1a** with 4-chloroaniline **6c** (79% ee, Entry 7) than with 4-methoxyaniline **6a** (37% ee, Entry 1).

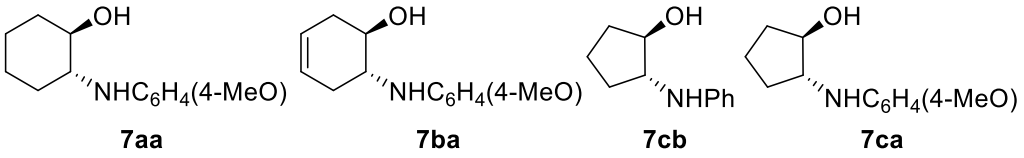
Table 2: Aminolysis of epoxides **1** catalyzed by complex Yb/**L2** or Pr/**L2**.



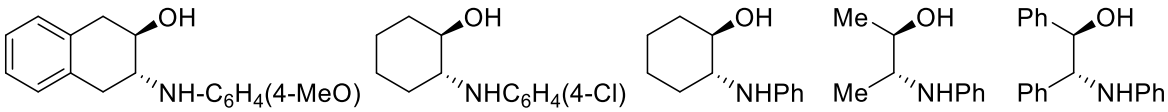
1 **6** **7**

Condition **A**: $Yb(OTf)_3$ (10 mol%), BINOL **L2** (12 mol%), Ph_2NBn (24 mol%), amine (1.2 eq.), toluene, 4Å MS, 0 to -78 °C

Condition **B**: $Pr(O\text{-}i\text{-}Pr)_3$ (10 mol%), BINOL **L2** (20 mol%), $Ph_3P{=}O$ (30 mol%), amine (1.2 eq.), toluene, 50 °C



7aa **7ba** **7cb** **7ca**



7ha **7ac** **7ab** **7db** **7ib**

Entry	Conditions	Epoxide **1**	Amine **6**	Aminoalcohol **7**	Yield (%)	ee (%)
1	**A**	**1a**	**6a**	**7aa**	64	37
2	**B**	**1a**	**6a**	**17a**	87	37
3	**B**	**1b**	**6a**	**7ba**	75	53
4	**A**	**1c**	**6b**	**7cb**	98	12
5	**B**	**1c**	**6a**	**7ca**	71	50
6	**B**	**1h**	**6a**	**7ha**	70	38
7	**A**	**1a**	**6c**	**7ac**	98	76
8	**A**	**1a**	**6b**	**7ab**	90	80
9	**A**	**1d**	**6b**	**7db**	99	43
10	**A**	**1i**	**6b**	**7ib**	92	17

For structure of ligand **L2** see Figure 3.

In 1990, Bolm *et al.* developed a bipyridine ligand **L3** (Figure 3), which was successfully used in a number of enantioselective reactions.[15,16] Schneider *et al.* used a catalyst prepared *in situ* from Bolm's ligand **L3** and $Sc(OTf)_3$ to catalyze aminolysis of *meso*-epoxides giving rise to β-amino alcohols **10** in high yields (49-96%) with enantioselectivities up to 97% (Table 3).[17,18] The best result was obtained when *cis*-stilbene oxide **1i** was reacted with phenylmethyl amine **6d** giving **7id** with 97% ee (Entry 9). Kobayashi *et al.* accomplished comparable results in water (91% ee) with 1 mol% catalyst loading based on scandium dodecyl sulphate (Entry 10).[19] It should be noted that no 1,2-diol formation was observed. Importantly, it was demonstrated that the reaction catalyzed by $Sc(OTf)_3$ with **L3** in water provided product **7id** in 85% ee, yet the yield was only 15% (not shown in Table 3). In the case of 2-*tert*-butylaniline **6e** and 2,6-dimethylaniline **6f** indium(III) triflate was especially suitable. Indeed, the desired products **7ie** and **7if** were synthesized with enantioselectivities up to 97% ee (Entries 17 and 18).[20] According to the X-ray analysis the active catalyst has the pentagonal-bipyramidal coordination geometry, where both pyridine nitrogens and the free hydroxy groups are bound to the scandium (Figure 2).[21]

Figure 2: X-ray of catalytic complex Sc/**L3**. Hydrogen atoms are omitted for clarity.[21]

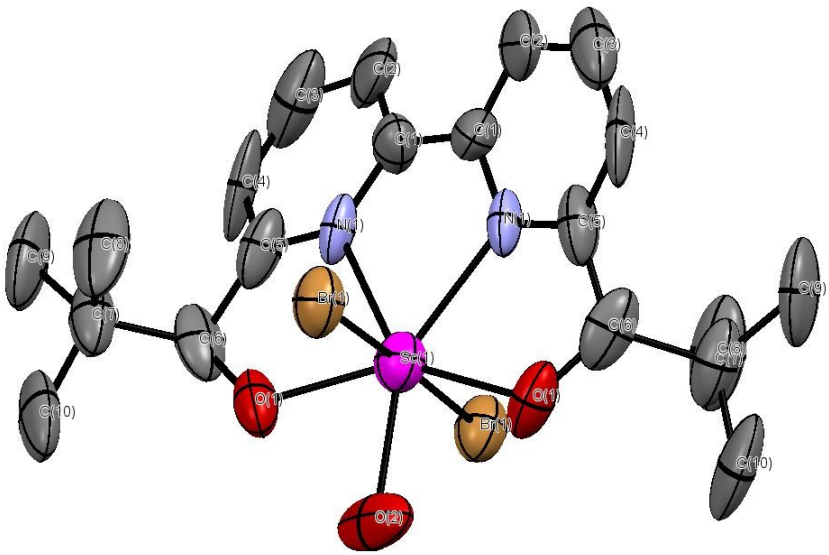
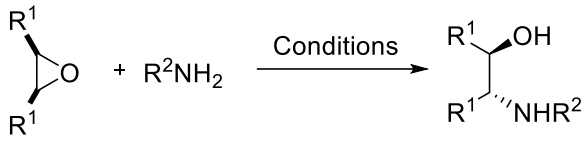
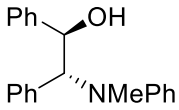


Table 3: Aminolysis of epoxides **1** catalyzed by complex Sc/**L3** or In/**L3**.

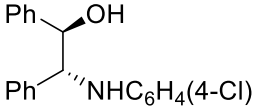


1 **6** **7**

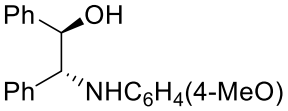
Condition **A**: $Sc(OTf)_3$ (10 mol%), **L3** (12 mol%), CH_2Cl_2, RT
Condition **B**: $Sc(DS)_3$ (1 mol%), **L3** (1.2 mol%), H_2O, RT
Condition **C**: $In(OTf)_3$ (10 mol%), **L3** (10 mol%), CH_2Cl_2, RT



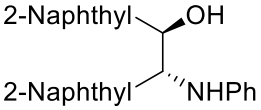
7id



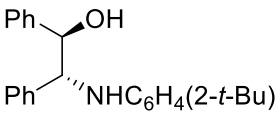
7ic



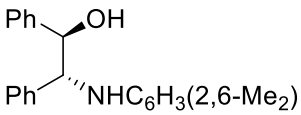
7ia



7jb



7ie



7if

For structures of other products see Table 2.

Entry	Condition	Epoxide **1**	Amine **6**	Aminoalcohol **7**	Yield (%)	ee (%)
1[a]	**A**	**1c**	**6b**	**7cb**	89	41
2[a]	**A**	**1a**	**6b**	**7ab**	96	54
3	**C**	**1a**	**6b**	**7ab**	91	31
4[b]	**A**	**1d**	**6b**	**7db**	92	60
5	**C**	**1d**	**6b**	**7db**	82	36
6	**A**	**1i**	**6b**	**7ib**	95	93
7	**B**	**1i**	**6b**	**7ib**	89	91
8	**C**	**1i**	**6b**	**7ib**	69	87
9	**A**	**1i**	**6d**	**7id**	85	97
10	**B**	**1i**	**6d**	**7id**	88	96
11	**C**	**1i**	**6d**	**7id**	80	92
12	**A**	**1i**	**6c**	**7ic**	94	95
13	**C**	**1i**	**6c**	**7ic**	95	90
14[b]	**A**	**1i**	**6a**	**7ia**	93	90
15	**A**	**1j**	**6b**	**7jb**	76	82
16	**B**	**1j**	**6b**	**7jb**	75	91
17	**C**	**1i**	**6e**	**7ie**	84	95
18	**C**	**1i**	**6f**	**7if**	82	97

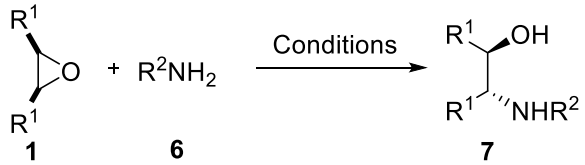
[a] Reaction carried out at -20 °C. [b] Reaction carried out at 0 °C. For structure of **L3** see Figure 3.

Furthermore, different catalytic systems were also studied (Table 4). Collins *et al.* showed that the ring-opening of aliphatic *meso*-epoxides can be catalyzed by complex **C2** (Figure 3),[22] in which gave higher enantioselectivities in the case of aliphatic products (Table 3). For instance, 1,2-amino alcohol **7ab** was prepared applying Sc/**L3** in 54% ee (Table 3, Entry 2). On the other hand, **7ab** prepared under conditions A was obtained with 91% ee (Table 4, Entry 3). To be concise, the results with aromatic epoxides are not reported.

In 2007, Kobayashi *et al.* published a protocol for aminolysis of *meso*-epoxides catalysed by a Niobium(V)/**L4** system[23] that was applicable to aliphatic epoxides, giving products **7** in 54-100% yield and 82-91% ee. Interestingly, the complex Nb/**L4** is less potent for ring-opening of alkyl acyclic epoxides, e.g. the reactions with *cis*-hex-3-ene oxide and *cis*-oct-4-ene oxide gave the corresponding products in less than 10% yields.

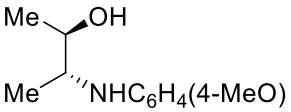
Recently, Kureshy *et al.* developed a Fe(III)/**L5** catalytic system. Aminolysis of *meso*-epoxides **1** with anilines **6** gave rise to products **7** with high enantioselectivities (up to 99%) and high yields (95%). The best result in terms of enantioselectivity (99%) was obtained in the reaction of *cis*-stilbene oxide **1i** with aniline **6b** (Table 4, Entry 9).[24] Authors claimed that the catalyst was recoverable and recyclable (5 times) with no decrease of its performance.

Table 4: Aminolysis of epoxides **1** catalyzed by complex **C2**, Nb/**L4** or Fe/**L5**.

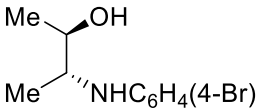


1 **6** **7**

Condition **A**: **C2** (10 mol%), CH_2Cl_2, -40 °C
Condition **B**: $Nb(OMe)_5$ (10 mol%), **L4** (11 mol%), toluene/CH_2Cl_2, 4Å MS, -15 °C
Condition **C**: $Fe(acac)_3$ (5 mol%), **L5** (2.5 mol%), CH_2Cl_2, RT



7da



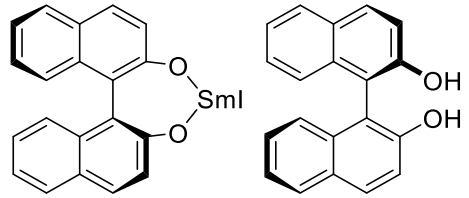
7dg

For structures of other products see Tables 2 and 3.

Entry	Condition	Epoxide **1**	Amine **6**	Product **7**	Yield (%)	ee (%)
1	**A**	**1c**	**6b**	**7cb**	76	76
2	**B**	**1c**	**6b**	**7cb**	59	86
3	**A**	**1a**	**6b**	**7ab**	79	91
4	**C**	**1d**	**6b**	**7db**	97	63
5	**B**	**1d**	**6b**	**7db**	100	94
6[a]	**B**	**1d**	**6a**	**7da**	99	90
7	**B**	**1d**	**6g**	**7dg**	98	95
8	**C**	**1d**	**6b**	**7db**	96	62
9	**C**	**1i**	**6b**	**7ib**	95	99
10	**C**	**1i**	**6c**	**7ic**	90	95
11	**C**	**1i**	**6a**	**7ia**	89	90

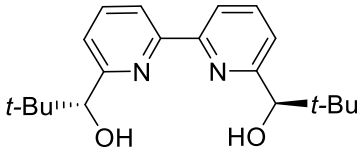
[a] Reaction carried out at 0 °C. For structure of **C2**, **L4** and **L5** see Figure 3.

Figure 3: List of catalyst and ligands mentioned in the section 2.1.2.

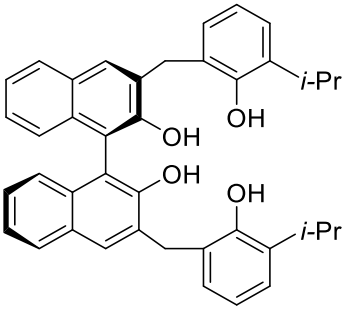


C2

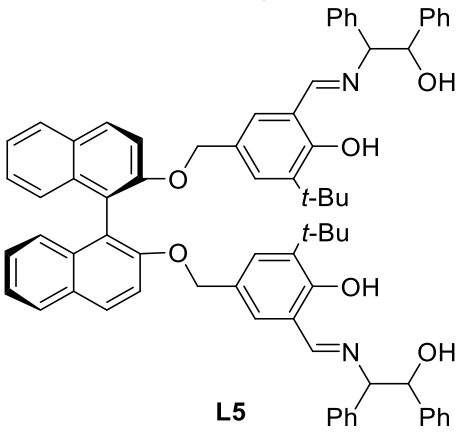
L2



L3



L4



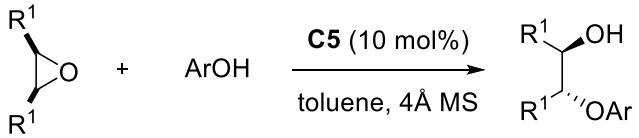
L5

2.2. Ring-opening with oxygen nucleophiles

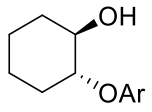
2.2.1. Ring-opening with phenol

Shibasaki *et al.* described an efficient catalytic enantioselective ring opening of various *meso*-epoxides with 4-methoxyphenol **8a** promoted by gallium-based heterobimetallic catalysts **C3** and **C4** (Figure 4).[25] Reactions catalyzed by catalyst **C3** gave rise to products with poor to moderate enantioselectivity (34-61% ee). Moreover, despite the use of 20 mol% catalyst loading did not lead to increase of enantioselectivity. Other attempts to increase yields and enantioselectivities were unsuccessful. Changing to catalyst **C4** led only to a slight increase of the yield while the enantioselectivity remained the same. Nevertheless, two years later Shibasaki *et al.* came up with another gallium(III) catalyst **C5** (Figure 4).[26] This catalyst **C5** turned out to be a better catalyst in terms of activity and enantioselectivity. The two previously mentioned catalysts **C3** and **C4** were probably inappropriate for this particular transformation because of undesirable ligand exchange with alcohol **8a**, causing decomposition of the catalyst. The improved linked-BINOL catalyst **C5** possesses a linker, which improves the reactivity and stability of the complex. Consequently, reactions catalyzed by complex **C5** with 10 mol% catalyst loading provided desired 1,2-diol monoethers in good yields (67-96%) with enantioselectivities up to 96% (Scheme 4). The reaction of cycloheptene oxide **1k**, however, resulted in a lower enantioselectivity of the product **9ka.**

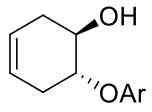
Scheme 4: Alcoholysis of epoxides **1** with alcohols **8a** catalyzed by **C5**.



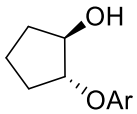
1 **8a**, Ar = 4-OMeC$_6$H$_4$ **9**



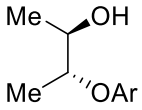
9aa, 72%, 91% ee



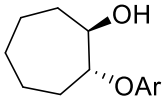
9ba, 94%, 85% ee



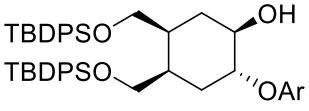
9ca, 88%, 85% ee



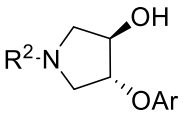
9da, 72%, 91% ee



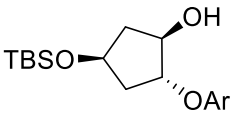
9ka, 82%, 66% ee



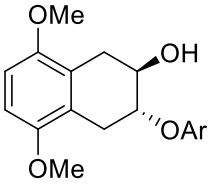
9la, 72%, 79% ee



9ma, 77%, 78% ee



9na, 67%, 87% ee



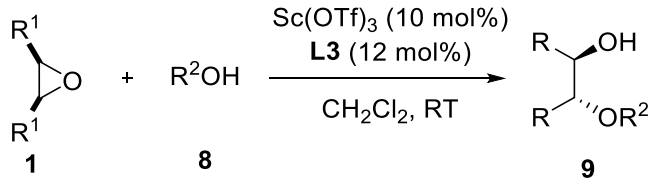
9oa, 85%, 96% ee

R^2 = 2,4,6-trimethylbenzenesulfonyl

2.2.2. Ring-Opening with alcohols

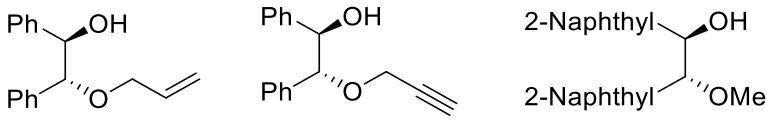
Schneider *et al.* studied also reactions of *meso*-epoxides with alcohols **8** using Sc(OTf)$_3$ as a catalyst with Bolm's ligand **L3**.[17,27] A broad range of alcohols **8** were applicable, therefore reactions of various epoxides **1** gave rise to ethers **9** in 33-93% yield and enantioselectivities up to 98% (Scheme 5). Nonetheless, aliphatic epoxides **1a**, **1d**, **1k**, **1q** gave only modest enantioselectivities (45-54% ee). A mechanistic study concerning the structure of the catalytic complex was also performed. After successful solving of the crystal structure of yttrium-bipyridine complex they found out that the coordination sense corresponds to the Kobayashi's one (Figure 2).[21] A catalytic complex composed of Sc(OTf)$_3$ with an analogue of Bolm's ligand **L6** (Figure 4) was tested in alcoholysis of *meso*-epoxide as well. The reaction of *cis*-stilbene oxide **1i** with alcohol **8b** in the presence of only 2 mol% catalyst loading of the Sc/**L6** complex gave product **9ib** with 98% ee.[28] On the other hand, **9ib** was obtained with 97% ee by using 10 mol% of the Sc/**L3** system. Obviously, the former is more efficient.

Scheme 5: Alcoholysis of epoxides **1** with alcohols **8** catalyzed by Sc/**L3**.

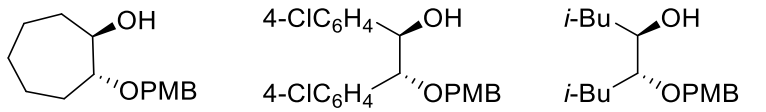


1 **8** **9**

9ab, 90%, 54% ee **9db**, 93%, 49% ee **9ib**, 82%, 97% ee **9ic**, 81%, 92% ee

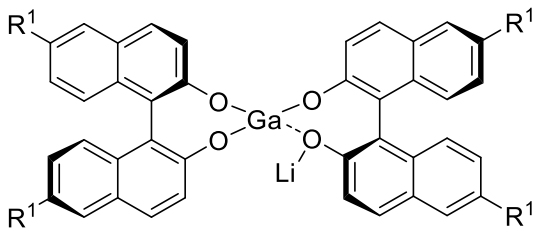


9id, 78%, 95% ee **9ie**, 73%, 91% ee **9jc**, 83%, 98% ee



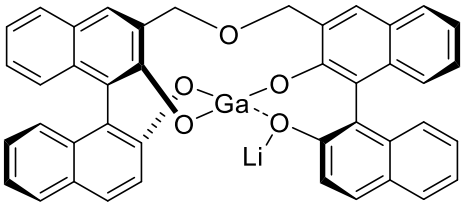
9kb, 46%, 53% ee **9pb**, 75%, 92% ee **9qb**, 33%, 45% ee

Figure 4: List of catalysts and ligands mentioned in the section 2.2.

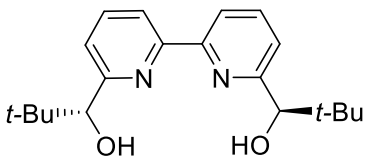


R1= H: **C3** (20 mol%)

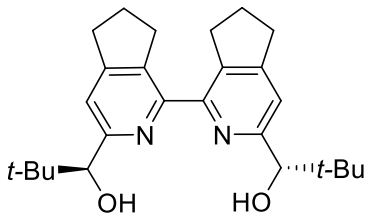
R1= SiEt3: **C4** (20 mol%)



C5 (10 mol%)



L3



L6

2.3. Ring-opening epoxides with sulphur nucleophiles

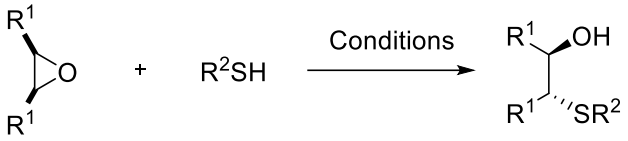
2.3.1. Ring-opening of *meso*-epoxides with thiols

Gallium(III) catalyst **C3** (Figure 6) was employed by Shibasaki *et al.* in thiolysis of *meso*-epoxides **1** with *tert*-butyl hydrosulphide **10a** yielding the desired 1,2-mercaptoalcohols **11** with enantioselectivities up to 98% ee (Table 5, Condition A).[29] The use of molecular sieves as an additive increased the yield although it did not affect the enantioselectivity (Entry 2). Unfortunately, the results suggest that the use of a bulky thiol is mandatory to suppress the undesirable ligand exchange of BINOL with thiols. In order to broaden the substrate scope of epoxides and thiols, many research groups attempted to develop various catalysts, such as chromium-salen,[30] titanium-salen[31] or heterobimetallic gallium-titanium-salen complexes.[32] The first highly enantioselective method for desymmetrization of *meso*-epoxides with thiophenol **10b** using Li-BINOL phosphate **C6** (Figure 6) was reported by Antilla *et al.* in 2014 (Table 5, Conditions B).[33] The resulting sulphides (*S,S*)-**11** were obtained with enantioselectivities up to 96%. Firstly, authors screened reactions of different epoxides **1** with thiophenol **10b** (Entries 3, 5, 9–11). Next, they explored the scope of the thiol nucleophiles, such as 4-methoxyphenylthiol **10c** or *t*-butylphenylthiol **10d** for ring-opening of epoxide **1b** affording **11bc** and **11bd** in 95% and 96% ee, respectively (Entries 6 and 7). It's worth noting that no products were formed when aliphatic thiols were employed.

In this fashion, Kobayashi *et al.* and Schneider *et al.* extended this protocol and showed that Bolm's ligand **L3** is an effective chiral ligand for this endeavor (Table 6).[34–36] The first example of successful utilization of thiophenols **10** in the presence of water and $Sc(DS)_3$ was described.[34] The corresponding sulphides **11** were isolated in moderate to good yields (66-76%) with high enantioselectivities (85-92% ee). In the following work, the desymmetrization of *meso*-epoxides **1** with thiols **10** was carried out in the presence of Sc/**L3** in dichloromethane, to afford respective sulphides **11** in moderate to good yields (41-87%) with high enantioselectivities up to 96%.[35] While all aromatic epoxides provided products with high enantioselectivities, the adduct **11dd** was obtained with only 50% ee (Entry 1). The authors alleged that it's caused by a competitive undesired non-catalyzed reaction, resulted in decreased enantioselectivity. Moreover, Schneider *et al.* disclosed an In/bipyridine complex catalyzed enantioselective ring-opening of *meso*-epoxides **1** with aliphatic and aromatic thiols **10** providing products **11** in good yields (76-91%) and excellent enantioselectivities (85-96% ee).[36] First and foremost, they identified the Indium(III) bromide/bipyridine complex as the most suitable one, which not only possessed sufficient Lewis acidity, but also tolerated the Lewis basic thiols **10**. Interestingly, the same

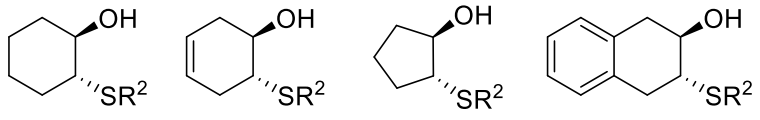
reaction catalyzed by indium(III) chloride took 6 days to finish, while the enantioselectivity remained the same (not shown in the Table 6). Thus, employing the $InBr_3$/**L3** system, there appears to be no structural or electronic limitation regarding the thiol component. In fact, straight-chain aliphatic thiols, such as an ethanethiol **10e** or *n*-butanethiol **10f**, also led to products with high enantioselectivity up to 95% ee (Entries 8 and 9). Nonetheless, aliphatic *meso*-epoxides gave rise to products with low enantiopurity (no further examples shown in the literature).

Table 5: Thiolysis of epoxides **1** catalyzed by **C3** and **C6**.

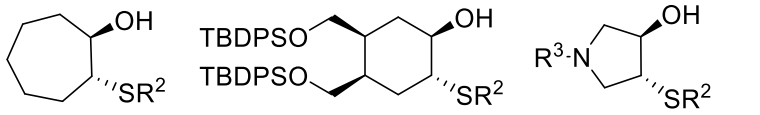


1 **10** **11**

Condition **A**: **C3** (10 mol%), toluene, 4Å MS, RT
Condition **B**: **C6** (10 mol%), 1,4-xylene, 4Å MS, RT



11a **11b** **11c** **11h**



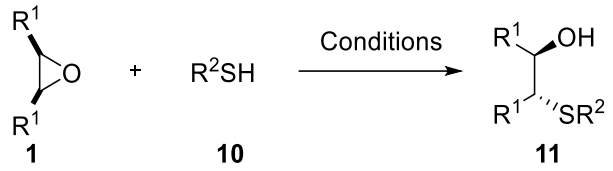
11k **11l** **11m**

R^3 = 2,4,6-trimethylbenzenesulfonyl

Entry	Conditions	Epoxide **1**	Thiol **10**	R^2	Product **11**	Yield (%)	ee (%)
1[a]	**A**	**1a**	**10a**	*t*-Bu	**11aa**	35	98
2	**A**	**1a**	**10a**	*t*-Bu	**11aa**	80	97
3	**B**	**1a**	**10b**	Ph	**11ab**	82	88
4	**A**	**1b**	**10a**	*t*-Bu	**11ba**	74	95
5	**B**	**1b**	**10b**	Ph	**11bb**	82	94
6	**B**	**1b**	**10c**	4-$MeOC_6H_4$	**11bc**	94	95
7	**B**	**1b**	**10d**	*t*-BuC_6H_4	**11bd**	95	96
8	**A**	**1c**	**10a**	*t*-Bu	**11ca**	89	91
9[b]	**B**	**1c**	**10b**	Ph	**11cb**	89	75
10	**B**	**1h**	**10b**	Ph	**11hb**	76	87
11[b]	**B**	**1k**	**10b**	Ph	**11kb**	45	84
12	**A**	**1l**	**10a**	*t*-Bu	**11la**	81	96
13	**A**	**1m**	**10a**	*t*-Bu	**11ma**	89	89

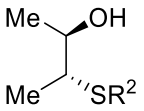
[a] Reaction carried out without 4Å MS. [b] 20 mol% catalyst was used. For structures of **C3** and **C6** see Figure 6.

Table 6: Thiolysis of epoxides **1** catalyzed by Sc/**L3** and In/**L3**.

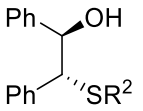


1 **10** **11**

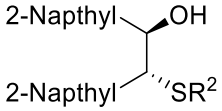
Condition **A**: $Sc(DS)_3$ (10 mol%), **L3** (12 mol%), H_2O, RT
Condition **B**: $Sc(OTf)_3$ (10 mol%), **L3** (12 mol%), CH_2Cl_2, RT
Condition **C**: $InBr_3$ (10 mol%), **L3** (11 mol%), CH_2Cl_2, RT



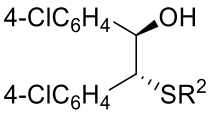
11d



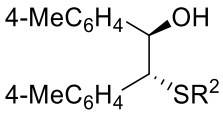
11i



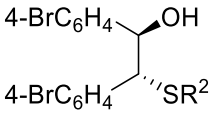
11j



11p



11r



11s

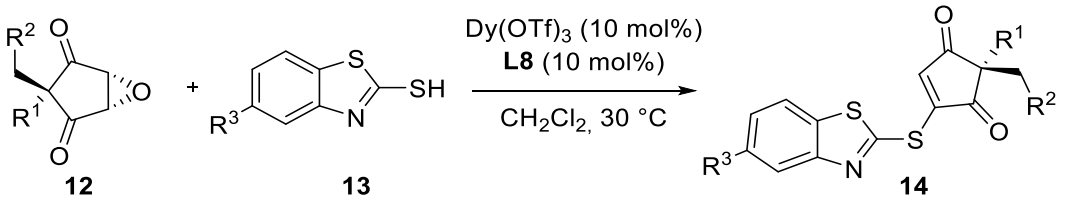
Entry	Condition	Epoxide **1**	Thiol **10**	R^2	Product **11**	Yield (%)	ee (%)
1	**B**	**1d**	**10d**	*t*-BuC_6H_4	**11dd**	41	50
2	**A**	**1i**	**10b**	Ph	**11ib**	73	89
3	**A**	**1i**	**10c**	4-$MeOC_6H_4$	**11ic**	66	87
4	**B**	**1i**	**10b**	Ph	**11ib**	87	95
5	**B**	**1i**	**10c**	4-$MeOC_6H_4$	**11ic**	79	95
6	**B**	**1i**	**10d**	*t*-BuC_6H_4	**11id**	87	95
7	**C**	**1i**	**10b**	Ph	**11ib**	80	92
8	**C**	**1i**	**10e**	Et	**11ie**	91	95
9	**C**	**1i**	**10f**	*n*-Bu	**11if**	90	95
10	**C**	**1j**	**10b**	Ph	**11jb**	79	96
11	**C**	**1p**	**10b**	Ph	**11pb**	84	92
12[a]	**B**	**1r**	**10c**	4-$MeOC_6H_4$	**11rc**	69	94
13	**C**	**1r**	**10b**	Ph	**11rb**	76	85
14	**A**	**1s**	**10a**	*t*-Bu	**11sa**	76	85
15	**A**	**1s**	**10d**	*t*-BuC_6H_4	**11sd**	69	92
16	**B**	**1s**	**10d**	*t*-BuC_6H_4	**11sd**	86	96

[a] Reaction carried out at 0 °C. For structure of **L3** see Figure 6.

2.3.2. Ring-opening of diketoepoxides with thiazoles

The usual group next to the epoxide carbon is either an alkyl or an aryl, but not a carbonyl group.[37] A lowered reactivity of diketoepoxides compared to the alkyl or aryl ones has been observed. In 2016, however, Wang *et al.* developed an unprecedented method for ring-opening of *meso*-diketoepoxides **12** giving a variety of cyclopentene-1,3-diones **14** with high enantioselectivities up to 94% (Table 7).[38] In the model reaction, diketoepoxide **12a** and benzothiazole **13a** were selected. The authors found out that the optimal reaction condition required to use the dysprosium(III) triflate/**L8** complex as a catalyst (Figure 6). Under these conditions, a spontaneous elimination process followed the ring-opening affording product **14aa** with 93% ee (Entry 1). After establishing the suitable reaction condition, the reaction scope was evaluated with respect to variously substituted diketoepoxides **12a-12d** (Entries 1-4) and thiazoles **13a-d** (Entries 5-7). The X-ray structure of compound **14aa** showed that the quaternary carbon had the *R* configuration (Figure 5).

Table 7: Asymmetric desymmetrization of diketoepoxides **12**.



Entry	Epoxide **12**	R^1	R^2	Thiol **13**	R^3	Product **14**	Yield (%)	ee (%)
1	**12a**	Me	Ph	**13a**	H	**14aa**	96	93
2	**12b**	Me	4-MeC_6H_4	**13a**	H	**14ba**	98	92
3	**12c**	Et	Ph	**13a**	H	**14ca**	97	92
4	**12d**	Me	4-$CF_3C_6H_4$	**13a**	H	**14da**	92	90
5	**12a**	Me	Ph	**13b**	Me	**14ab**	97	94
6	**12a**	Me	Ph	**13c**	OMe	**14ac**	92	94
7	**12a**	Me	Ph	**13d**	Cl	**14ad**	87	90

For structure of **L8** see Figure 6.

Figure 5: X-ray of compound **17aa**.[38]

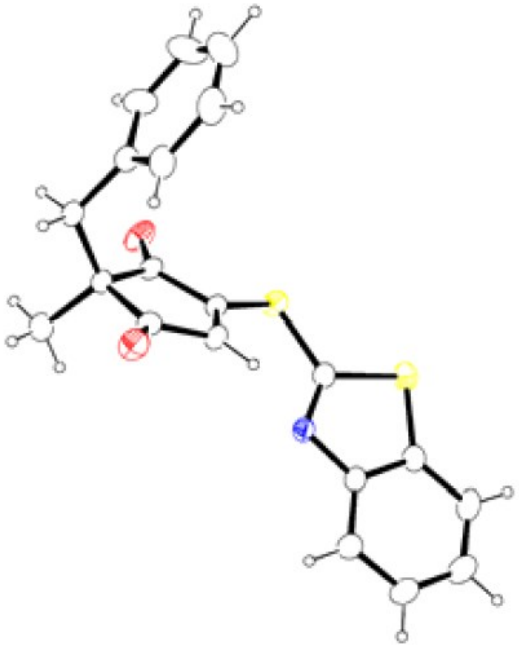
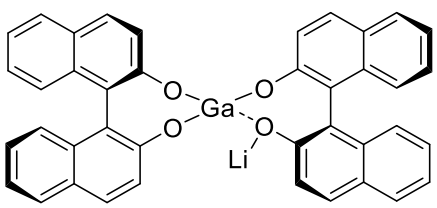
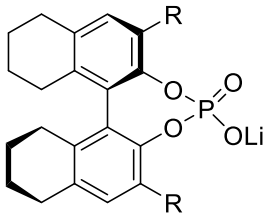


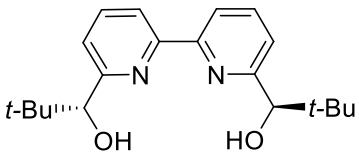
Figure 6: List of catalysts and ligands mentioned in the section 2.3.



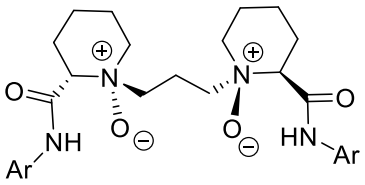
C3



C6, R = 2,4,6-*i*-$Pr_3C_6H_2$



L3

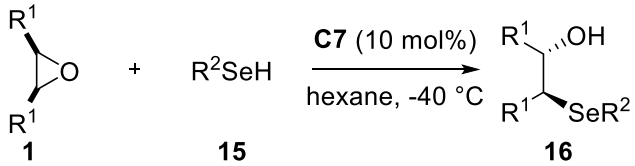


L8; Ar = 2,4,6-*i*-$Pr_3C_6H_2$

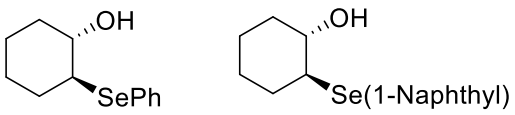
2.4. Ring-opening with selenium nucleophiles

In 2005, Zhu *et al*. published the first protocol for desymmetrization of *meso*-epoxides with phenylselenol **15a** and 1-selenonaphthol **15b** using heterobimetallic titanium(II)-gallium(III)(salen) complex **C7** (Figure 7). Various epoxides **1** were opened in typically very good yields (70-94%) and enantioselectivities in the range from 55 to 97% ee (Scheme 6).[39] The heterobimetallic catalyst appears to act as a multifunctional catalyst containing two different metals that should work synergistically. It's possible that the hard Lewis acid titanium metal activates the epoxide moiety. At the same time, the relatively soft Lewis acid gallium metal coordinates the selenol nucleophile. By virtue of this, selenophenol attacks more efficiently and selectively the epoxide ring.

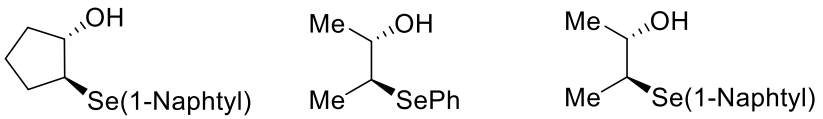
Scheme 6: Selenolysis of epoxides **1** catalyzed by **C7**.



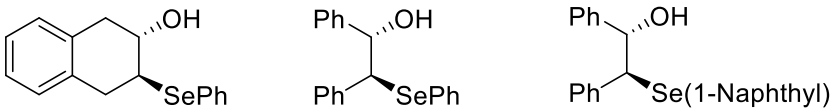
1 **15** **16**



16aa, 94%, 97% ee **16ab**, 93%, 78% ee **16ca**, 85%, 94% ee



16cb, 80%, 70% ee **16da**, 87%, 87% ee **16db**, 73%, 75% ee



16ha, 92%, 90% ee **16ia**, 70%, 72% ee **16ib**, 70%, 55% ee

Schneider *et al.* benefited from using the Sc/**L3** complex[40] to open several *meso*-epoxides **1** with phenylselenol **15a** resulting in 1,2-selenoalcohols **16** in 51-77% yields and up to 94% ee (Table 8). In the model reaction, *cis*-stilbene oxide **1i** was treated with phenylselenol **15a** and Sc/**L3** (10 mol%) resulting in formation of the selenol adduct **16ia** in 60% yield and 93% ee along with 20% of the corresponding deselenated carbinol **17ia** (Entry 1). The authors took advantage of this result and carried out other reactions. Having in mind that the deselenation proceeded presumably in a radical manner,[41] the authors performed the same reaction with careful exclusion of oxygen and light. Indeed, the 1,2-selenoalcohol **16ia** was then obtained in 77% yield and 93% ee (Entry 2). Afterwards, series of 1,2-selenoalcohols **16** were prepared under condition A, as well as deselenated carbinols **17** under condition B. One can say that since the carbinols **17** are obtained from the 1,2-selenoalcohols **16** they should have been formed with the same enantioselectivity. However, the slight decrease of enantioselectivities of some carbinols **17** in comparison with corresponding 1,2-selenoalcohols **16** have been observed (Entries 4-7). Perhaps the hydrogen abstraction at the benzylic carbinol center during radical process causes partial racemization.

Figure 7: List of catalyst and ligand mentioned in the section 2.4.

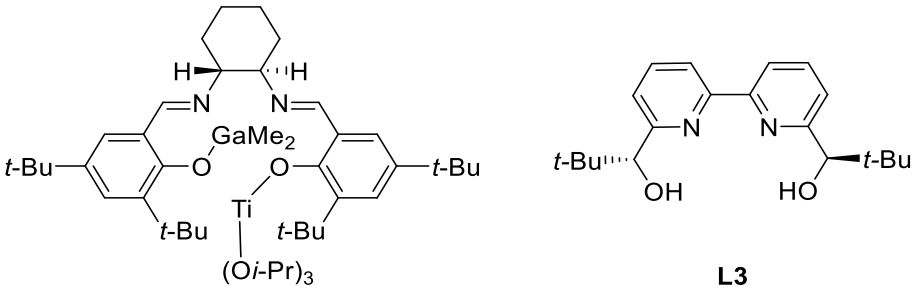
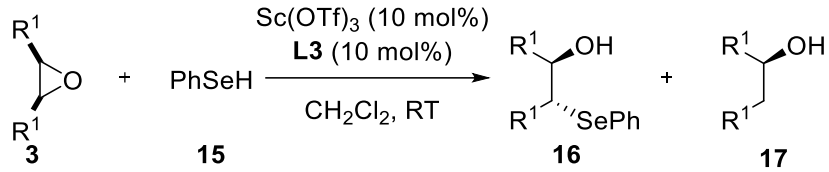


Table 8: Selenolysis of epoxides **1** catalyzed Sc/**L3**.



Condition **A**: reaction in the dark with degassed solvent.
Condition **B**: reaction with reagent-grade solvent under daylight.

Entry	Condition	Epoxide **1**	R^1	Alcohol **16**	Yield (%)	ee (%)	Carbinol **17**	Yield (%)	ee (%)
1	-	**1i**	Ph	**16i**	60	93	**17i**	20	92
2	A	**1i**	Ph	**16i**	77	93	**17i**	<5	92
3	B	**1i**	Ph	**16i**	6	ND	**17i**	60	90
4	A	**1p**	4-ClC_6H_4	**16p**	51	89	**17p**	17	85
5	B	**1p**	4-ClC_6H_4	**16p**	10	89	**17p**	64	87
6	A	**1r**	4-MeC_6H_4	**16r**	54	94	**17r**	18	86
7	B	**1r**	4-MeC_6H_4	**16r**	<5	94	**17r**	64	92
8	A	**1s**	4-BrC_6H_4	**16s**	64	91	**17s**	5	91
9	B	**1s**	4-BrC_6H_4	**16s**	12	92	**17s**	64	92

ND = not determined. For structure of **L3** see Figure 7.

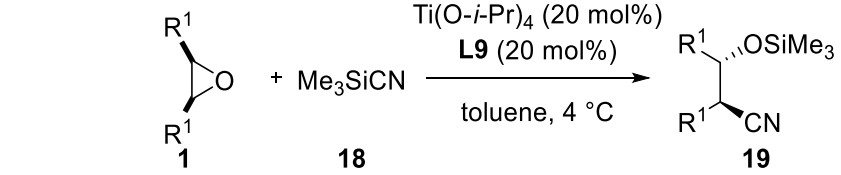
2.5. Ring-opening of epoxides with carbon nucleophiles

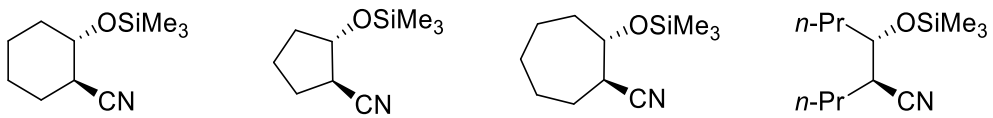
Opening of epoxides using variety of carbon-based nucleophiles is a powerful method for constructing C–C bonds. This approach may be used in many syntheses, especially if it is a stereo-controlled process.

2.5.1. Ring-opening of epoxides with cyanide

Ring opening of *meso*–epoxides **1** with trimethylsilyl cyanide **18** affording β-trimethylsilyloxy nitriles **19** was studied by Snapper *et al.* (Scheme 7).[42] Reactions were catalyzed by titanium(IV)/Schiff base complexes with good enantioselectivities (78-87%). Identification of substrate-specific catalysts differs in this study from conventional protocols, in which each single metal/ligand complex combination is selected and then matched to a range of substrates. From the initial studies, it was suspected that the asymmetric induction is affected by the subtle structure of epoxides.[43] In other words, each epoxide required a distinct ligand structure for optimal enantioselectivity. In the following example, ring-opening of cyclohexene oxide **1a** afforded product **19a** with 87% ee using ligand **L9a**, which contains a 3-fluoro-2-hydroxyphenyl component. Whereas ligand **L9b** is suitable ring-opening of **1c** (83% ee). For seven-membered epoxides **1k** and acyclic epoxide **1t**, the highest level of enantioselectivities was obtained with Schiff bases **L9c** (**19k**, 84% ee) and **L9d** (**19t**, 78% ee), respectively. For all the structures of ligands **L9a-d** see Figure 8.

Scheme 7: Ring-opening of **1** with trimethylsilyl cyanide **18** catalyzed by Ti/**L9**.

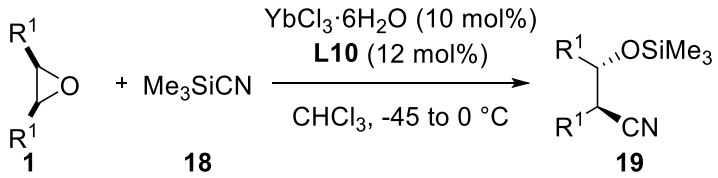


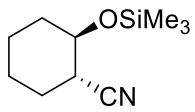


ligand: **L9a** **19a**, 65%, 87% ee | ligand: **L9b** **19c**, 72%, 83% ee | ligand: **L9c** **19k**, 68%, 84% ee | ligand: **L9d** **19t**, 69%, 78% ee

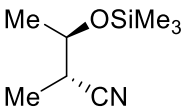
Another example of a catalytic system for above mentioned reaction was developed by Jacobsen *et al.*[44] Ring-opening of *meso*-epoxides **1** with trimethylsilyl cyanide **18** catalyzed by Yb/**L10** afforded β-trimethylsilyloxy nitriles **19** in both in high yields (72-90%) and enantioselectivities up to 92% (Scheme 8). As a matter of fact, two PyBOX ligands **L10** were utilized depending on the structure of epoxide. In case of epoxides **1a** and **1d** the phenyl substituted ligand **L10a** provided the best enantioselectivities (both 90%). On the other hand, the use of ligand **L10b** bearing the *t*-Bu fragment enabled to obtain product **19c**, **19g** and **19u** with high enantioselectivities (83-92% ee). It is noteworthy that the absolute configuration of compounds **19a** and **19d** were opposite to the **19c**, **19g** and **19u**, even though the absolute configuration of ligands was the same.

Scheme 8: Ring-opening of **1** with cyanide **18** catalyzed by Yb/**L10**.

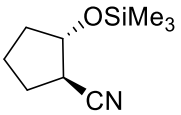




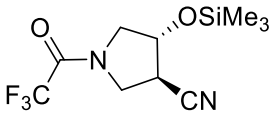
Ligand: **L10a**
19a, 90%, 91% ee



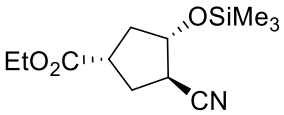
Ligand: **L10a**
19d, 80%, 90% ee



Ligand: **L10b**
19c, 83%, 92% ee

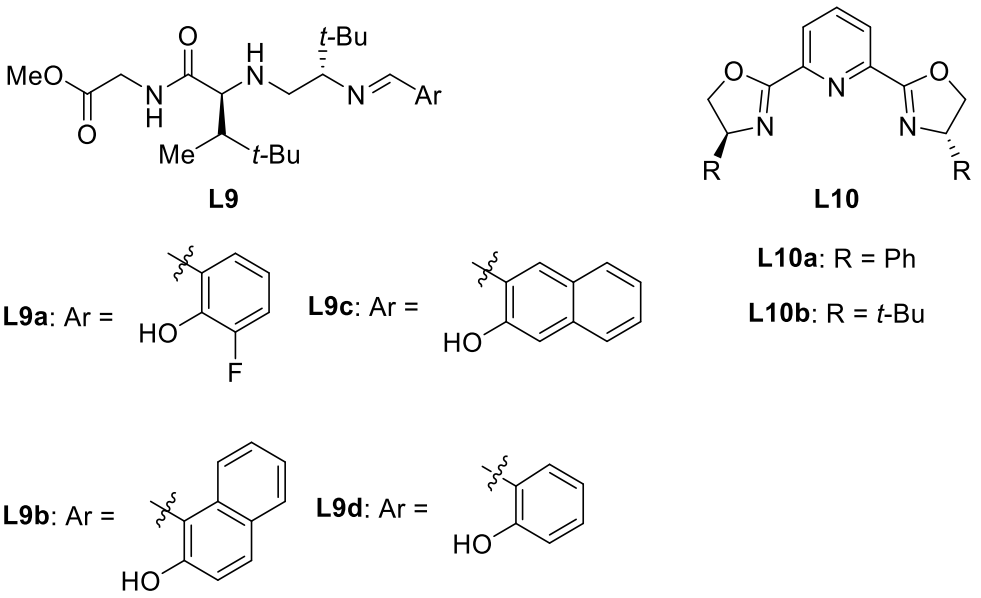


Ligand: **L10b**
19g, 72%, 87% ee



Ligand: **L10b**
19u, 86%, 83% ee

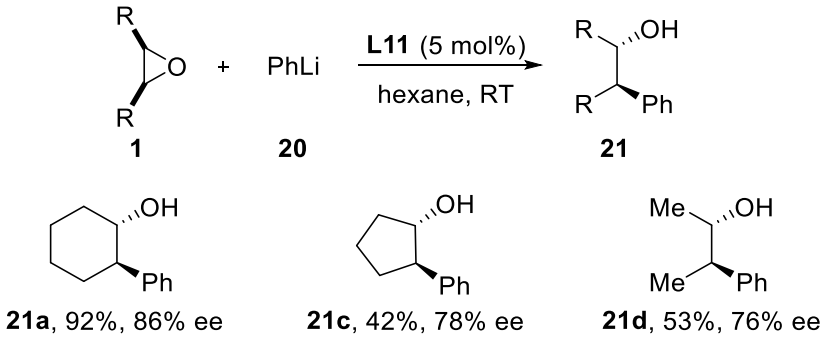
Figure 8: Ligands mentioned in the section 2.5.1.



2.5.2. Ring-opening of epoxides with organolithium compound

Oguni *et al.* reported the first catalytic protocol for desymmetrization of epoxides **1** with phenyllithium **20**.[45] Three *meso*-epoxides were treated with phenyl lithium along with **L11** affording adducts **21** (Scheme 9). Only 5 mol% loading of chiral Schiff-based ligand **L11** (Figure 10) was enough sufficient for achieving good enantioselectivities (76-86% ee). Although the yields of **21c** (42%) and **21d** (53%) were somewhat mediocre.

Scheme 9: Ring-opening of **1** with phenyl lithium in the presence of **L11**.

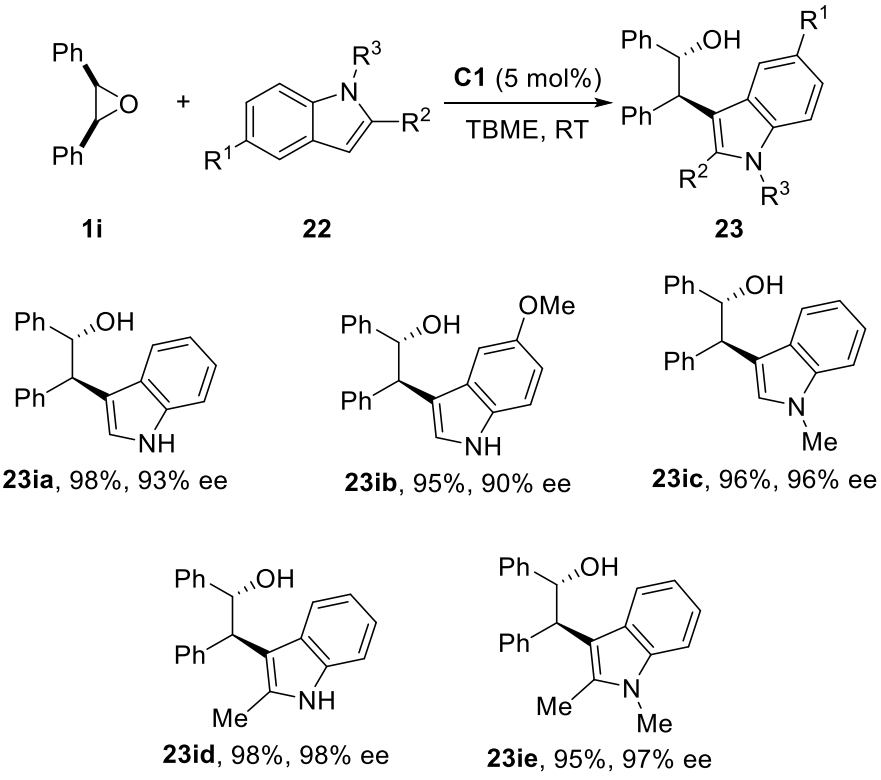


2.5.3. Ring-opening of epoxides with indoles

Indole moieties have been included in many total syntheses, due to the fact that their motifs are often seen in natural products and bioactive molecules.[46] One way how to functionalize indole is a reaction with *meso*-epoxides.

One example of such transformation was reported by Umani-Ronchi *et al.* with chromium(III)(salen) complex **C1** (Figure 1).[47] Epoxide **1i** reacted with 5 different indoles **22** giving products **23** in 90-98% ee and in 95-98% yield (Scheme 10).

Scheme 10: Ring-opening of **1** with indoles **22** catalyzed by **C1**.



The enantioselective ring-opening of epoxides with indoles has been also carried out with metal/**L3** complexes. Kobayashi *et al.* used the Sc/**L3** system to catalyze reactions of *meso*-epoxides **1** with indoles **22** in water at room temperature and obtained the respective products **23** with enantioselectivities in the region of 85-93% ee (Table 9).[34,48,49] The reactions proceeded with respect to a number of variously 5-substituted indoles **22** (Entries 1, 4, 7 and 10). Interestingly, when the Cu(II)/**L3** system was used, the products **23** with the opposite configuration were formed (Entries 2, 5, 8, 11, 13, 16 and 18). The observed difference in configuration can be ascribed to the divergence in coordination of the metals to the ligand **L3**. In the contrast to the X-ray structure of the Sc/**L3** complex (Figure 2), in the Cu/**L3** complex two

pyridines and only one hydroxyl group are coordinated to the copper atom in the tridentate manner (Figure 9). This protocol is, however, limited to reactions in water. Performing the desymmetrization in organic solvents gave unsatisfactory results (Entries 19 and 20). Additionally, reactions with aliphatic epoxides, such as **1a** or **1d,** delivered only traces of the expected products (Entries 21 and 22). Ollevier *et al.* reported a procedure utilizing the Fe/**L3** system that afforded the corresponding products **23** with excellent enantioselectivities up to 99% (Entries 3, 6, 9, 12 and 14).[50]

Figure 9: X-ray structure of Cu/**L3** and Sc/**L3**. Hydrogen atoms are omitted for clarity.[48]

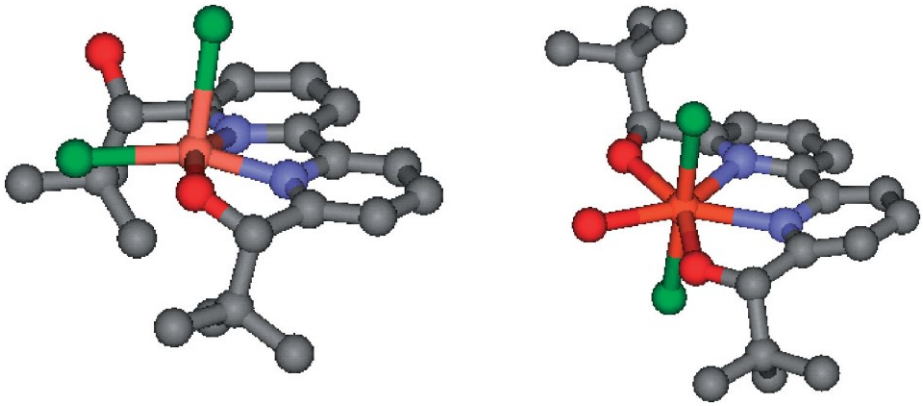
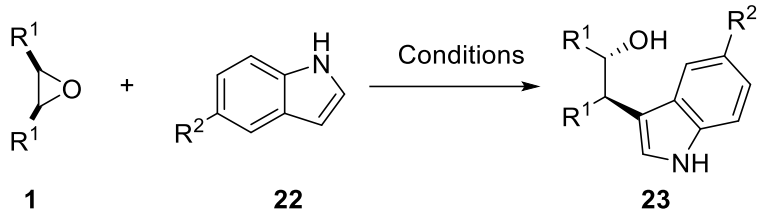


Table 9: Ring-opening of **1** with indoles **22** catalyzed by Sc/**L3** and Cu/**L3**.



1 **22** **23**

Condition A: $Sc(DS)_3$ (5 mol%), **L3** (6 mol%), H_2O, RT
Condition B: $Cu(O_3SC_{11}H_{23})_2$, (5 mol%) **L3** (6 mol%), H_2O, RT
Condition C: $Fe(ClO_4)\cdot 6H_2O$ (10 mol%), **L3** (12 mol%), CH_2Cl_2, 4Å MS, 22 °C

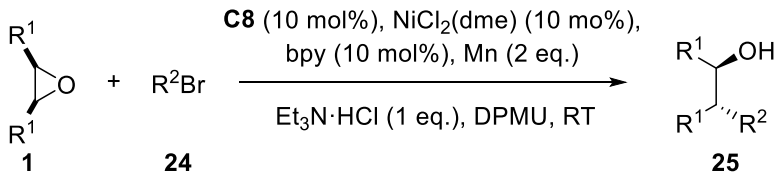
Entry	Condition	Epoxide **1**	R^1	Indole **22**	R^2	Product **23**	Yield (%)	ee (%)
1	A	**1i**	Ph	**22a**	H	**23ia**	85	93
2	B	**1i**	Ph	**22a**	H	**23ia**	80	-96
3	C	**1i**	Ph	**22a**	H	**23ia**	90	99
4	A	**1i**	Ph	**22b**	OMe	**23ib**	75	92
5	B	**1i**	Ph	**22b**	OMe	**23ib**	45	-92
6	C	**1i**	Ph	**22b**	OMe	**23ib**	80	99
7	A	**1i**	Ph	**22f**	Me	**23if**	71	85
8	B	**1i**	Ph	**22f**	Me	**23if**	81	-92
9	C	**1i**	Ph	**22f**	Me	**23if**	99	99
10	A	**1i**	Ph	**22g**	Br	**23ig**	59	90
11	B	**1i**	Ph	**22g**	Br	**23ig**	58	-90
12	C	**1i**	Ph	**22g**	Br	**23ig**	87	99
13	B	**1j**	2-Napthyl	**22a**	H	**23ja**	53	-85
14	C	**1j**	2-Napthyl	**22a**	H	**23ja**	80	96
15	A	**1r**	4-MeC_6H_4	**22a**	H	**23ra**	62	86
16	B	**1r**	4-MeC_6H_4	**22a**	H	**23ra**	43	-84
17	A	**1s**	4-BrC_6H_4	**22a**	H	**23sa**	59	93
18	B	**1s**	4-BrC_6H_4	**22a**	H	**23sa**	53	-92
19[a]	B	**1i**	Ph	**22g**	Br	**23ig**	Traces	-
20[a]	B	**1r**	4-MeC_6H_4	**22a**	H	**23ra**	Traces	-
21	B	**1a**	-$(CH_2)_4$-	**22a**	H	**23aa**	Traces	-
22	B	**1d**	Me	**22a**	H	**23da**	Traces	-

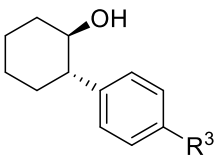
[a] Reaction carried out with $Cu(OTf)_2$ in CH_2Cl_2. For structure of ligand **L3** see Figure 10.

2.5.4. Ring-opening of *meso*-epoxides with aryl bromides

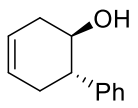
In 2015, Weix *et al.* reported the first enantioselective arylation of *meso*–epoxides catalyzed by the combination of (bpy)$NiCl_2$ with the chiral titanocenes.[51] Screening of the catalysts in the reaction of epoxide **1a** with phenyl bromide **24a** the best yield was obtained as well as enantioselectivity (**25aa**, 93%, 80% ee) when the chiral menthol-derived titanocene **C8** was employed as a chiral additive (Figure 10). This condition proved to be general for opening of *meso*-epoxides with aryl bromides. Hence, **25aa-ad** were obtained with enantioselectivities in the range of 78-82% (Scheme 11). Reactions of phenyl bromide **24a** with epoxides **1b** and **1e** provided products with high enantioselectivities (**25ba**, 93% and **25ea**, 95%, respectively). Whereas, epoxides **1c**, **1h** and **1k** afforded products **25ca**, **25ha** and **25ka** with lower enantioselectivities in the range of 84-87%. Surprisingly, *cis*-stilbene oxide **1i** did not react under this condition at all. Chemoselective arylation *via* cleavage of the C-Br bond in 4-bromophenyl triflate **24e** and 1-bromo-4-chlorobenzene **24f** was observed giving the respective products **25be** and **25cf** with good enantioselectivities (87 and 94% ee, respectively), as long as the reactions were not permitted to run past full conversions.

Scheme 11: Enantioselective arylation of epoxides **1** catalyzed by **C8**.

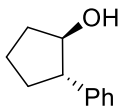




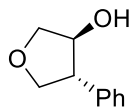
25aa: R^3 = H, 93%, 80% ee
25ab: R^3 = OMe, 70%, 78% ee
25ac: R^3 = CO_2Me, 82%, 84% ee
25ad: R^3 = C(O)Me, 59%, 82% ee



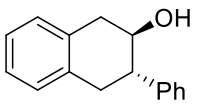
25ba, 99%, 93% ee



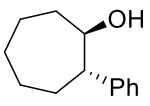
25ca, 89%, 87% ee



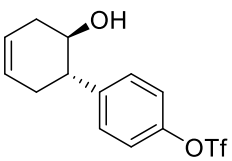
25ea, 91%, 95% ee



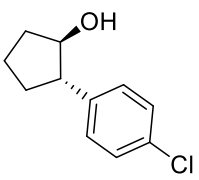
25ha, 77%, 87% ee



25ka, 72%, 84% ee



25be, 87%, 87% ee



25cf, 91%, 94% ee

2.5.5. Carbonylation of *meso*-epoxides to β-lactones

β-Lactone moieties have been included as a precursor in many synthesis, which are leading to many natural compounds.[52] The most direct formation of β-lactones involves the reaction of the ketenes with an aldehyde, which proceeds *via* [2+2] cycloaddition. The ring-expansion carbonylation of epoxides to β-lactones is an attractive alternative to the previously mentioned strategy. Moreover, epoxides are more readily available than ketenes. Ibrahim *et al.* provided such a transformation of *meso*-epoxides to β-lactones using the catalytic carbonylation.[53] Authors decided to use the $Co_2(CO)_8$/**C1** complex for an evaluation of a substrate scope (Scheme 12). The reaction of epoxide **1c** provided lactone **26c** in good yield (89%), although with low enantioselectivity (40%). The best result was obtained in the carbonylation of epoxide **1d**, affording product **26d** in 93% yield with 56% ee. 7-membered epoxides **1k** and **1v** (the *N*-tosyl-2,3,6,7-tetrahydroazepine derived epoxide) gave product **26k** (4% ee) and **26v** (31% ee). Comparable, but low enantioselectivities, were obtained in the case of 8-membered lactone **26w** and 12-membered lactone **26x** (11% and 13%, respectively).

Scheme 12: Ring-expansion carbonylation of epoxides **1**.

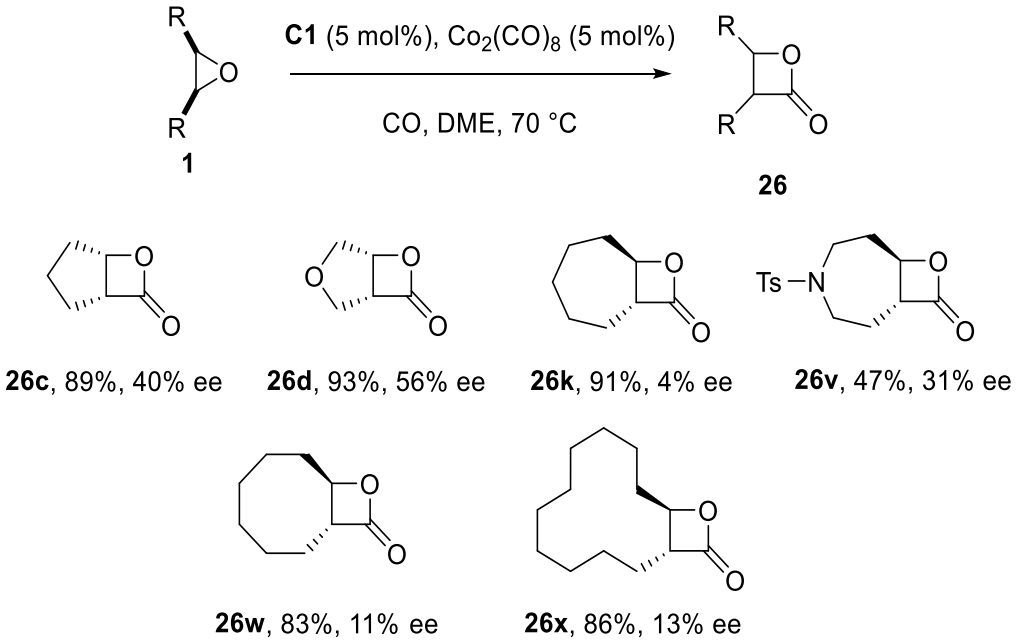
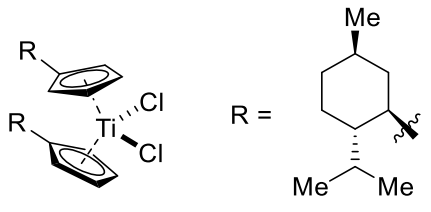
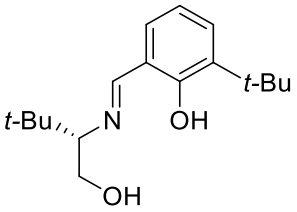


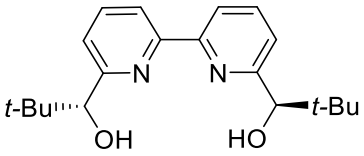
Figure 10: Catalysts mentioned in the sections 2.5.2, 2.5.3, 2.5.4 and 2.5.5.



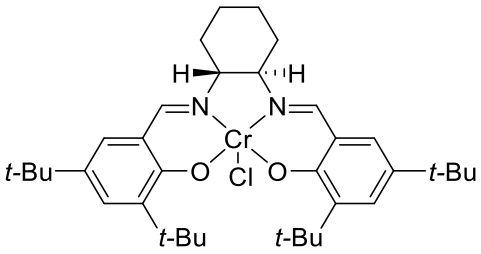
C8



L11



L3



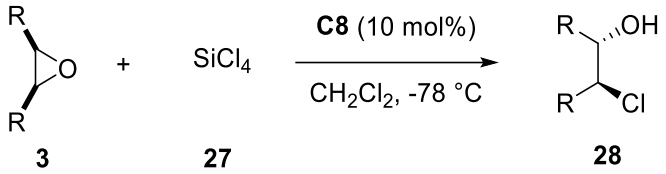
C1

2.6. Ring-opening with halogen nucleophiles

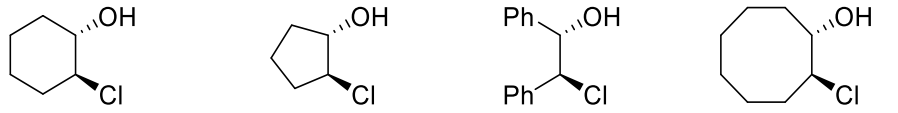
2.6.1. Ring-opening of epoxides with chloride anion

Dennmark *et al.* studied opening of epoxides **1** with tetrachlorosilane **27**.[54] A combination of **C8** (Figure 11) and **27** in dichloromethane at -78 °C was chosen as the standard reaction conditions. Under this condition epoxides **1** afforded chlorohydrins **28** (Scheme 13). Reactions of aliphatic epoxides, such as **1a**, **1c** and **1w** proceeded in poor enantioselectivity (**28a**, 51%; **28c**, 7%; **28w**, 2%). On the other hand, the reaction with *cis*-stilbene oxide **1i** provided desired product **28i** in 94% yield with 87% ee.

Scheme 13: Ring-opening of epoxides **1** with **27** catalyzed by **C8**.



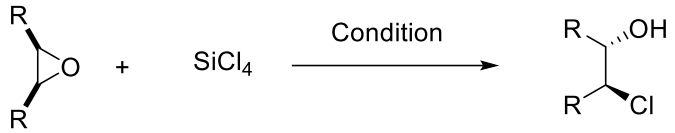
3 **27** **28**



28a, 90%, 51% ee **28c**, 87%, 7% ee **28i**, 95%, 87% ee **28w**, 95%, 2% ee

Next, Fu *et al.* discovered that planar-chiral pyridine-*N*-oxide **C19** efficiently catalyzes reactions of various aryl *meso*-epoxides **1** with tetrachlorosilane **27** (Table 10).[55] The enantiomeric excesses of products **28** were from high to excellent (91-98%, Entries 1, 3-6). However, alkyl epoxide **1zc** afforded modest enantioselectivity (**28zc**, 50%, Entry 7). Regarding epoxides **1i** and alkyl epoxide **1zc**, Nakajama *at al.* obtained similar results by using chiral *N,N*-dioxide **C10** (Entries 2 and 8).[56] It is noteworthy that the ring-opened product **28a** was obtained as a racemic mixture (Entry 9).

Table 10: Ring-opening of epoxides **1** with **27** catalyzed by **C9** or **C10**.



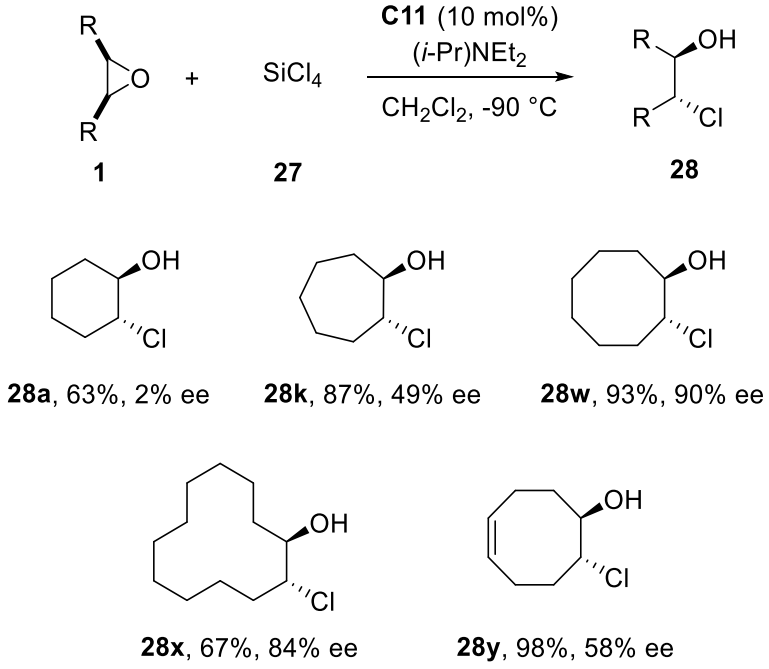
1 **27** **28**

Condition A: **C9** (5 mol%), (*i*-Pr)$_2$NEt, CH_2Cl_2, -85 °C
Condition B: **C10** (10 mol%), (*i*-Pr)$_2$NEt, CH_2Cl_2, -78 °C

Entry	Condition	Epoxide **1**	R	Product **28**	Yield (%)	ee (%)
1	A	**1i**	Ph	**28i**	88	94
2	B	**1i**	Ph	**28i**	95	90
3	A	**1j**	2-Naphthyl	**28j**	84	94
4	A	**1r**	4-$CH_3C_6H_4$	**28r**	94	93
5	A	**1za**	4-FC_6H_4	**28za**	97	91
6	A	**1zb**	4-$CF_3C_6H_4$	**28zb**	93	98
7	A	**1zc**	$BnOCH_2$	**28zc**	90	50
8	B	**1zc**	$BnOCH_2$	**28zc**	98	74
9	B	**1a**	-$(CH_2)_4$-	**28a**	83	0

Finally, opening alkyl epoxides **1** proceeded well with high enantioselectivities with PINDOX **C11** (Figure 11).[57] On one hand, cyclooctene oxide **1w** and cyclododecene oxide **1x** gave products **28w** in 90% ee and **28x** in 84% ee, respectively (Scheme 14). On the other hand, cyclohexene oxide **1a** gave poor enantioselectivity (**28a**, 2%) again. Products **28k** and **28y** were obtained in moderate enantioselectivity (49 and 58%).

Scheme 14: Ring-opening of epoxides **1** with **27** catalyzed by **C11**.



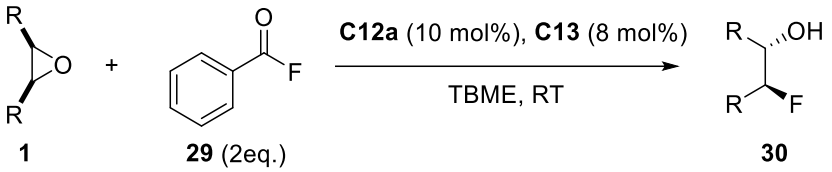
2.6.2. Ring-opening of epoxides with fluoride anion

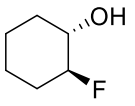
Formation of a C–F bond is a rather difficult task. The fluoride anion in protic media is more likely to be solvated than to act as a nucleophile. The key is to find efficient catalysts and a suitable fluoride sources that permit mild reaction conditions.

Introduction of fluorine atom *via* enantioselective opening of epoxides with silver fluoride mediated by (salen)chromium(III) complex **C1** (Figure 1) was studied by Haufe *et al.*[58] However, the use of up to 100 mol% of the complex was required to obtain just moderate enantioselectivities. Later, Doyle *et al.* reported the same reaction catalyzed by (salen)cobalt(II) complex **C12a** (Figure 11).[59] The source of the fluoride was in this case benzoyl fluoride. The presence of (-)-tetramisole **C13** (Figure 11) was also necessary in order to obtain β-fluorohydrin **30a** formation in 64% yield with 77% ee. Otherwise, only 52% ee was observed without **C13**. Furthermore, the enantioselectivity was improved by using (salen)cobalt(III)OTs **C12b** in *tert*-amyl alcohol to 93% ee. However, the **C12a** proved to be the optimal catalyst for epoxides

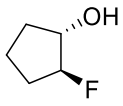
1c, **1k**, **1y** and **1z**. The corresponding β-fluorohydrins **30** were obtained with enantioselectivities up to 95% ee (Scheme 15). Five- (**1c**), seven- (**1k**), and eight-membered (**1y**) cyclic epoxides can be used as well-tolerated. On the contrary, epoxide **1z** undergoes the reaction with lower enantioselectivity (**30z**, 55%, 58% ee).

Scheme 15: Ring-opening of epoxides **1** with benzoyl fluoride **29** catalyzed by **C12**.

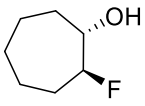




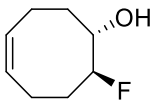
30a[a], 65%, 93% ee



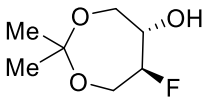
30c[b], 77%, 85% ee



30k, 82%, 90% ee



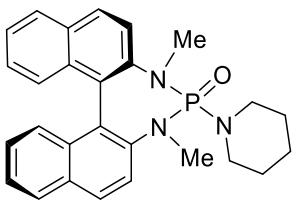
30y, 87%, 95% ee



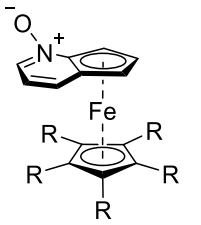
30z, 55%, 58% ee

[a] Reaction carried out with **C12b** in *tert*-amyl alcohol. [b] Reaction carried out in Et_2O.

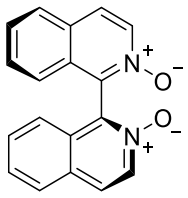
Figure 11: Catalysts mentioned in the section 2.6.



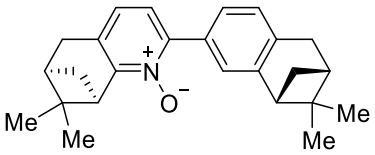
C8



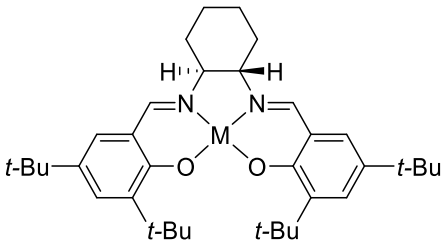
R = 3,5-$Me_2C_6H_3$
C9



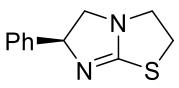
C10



C11



C12a: M = Co(II)
C12b: M = Co(III)OTs



C13

3. Aims of the Project

The ring-opening reaction of different *meso*-epoxide **1** was studied in this master thesis. The study was based on the results obtained in our group using ligand **L6** in the in complex metal catalyzed reactions. The aims of the master thesis are as follows:

i. To study ring-opening reactions of *cis*-stilbene oxide **1i** with various benzyl alcohols **8** by using the Sc/**L6** catalytic system.

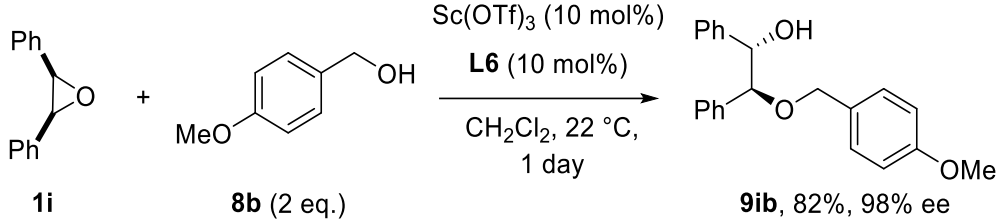
ii. To study reactions of aliphatic *meso*-epoxides with benzyl alcohol **8b** by using the Sc/**L6** catalytic system.

iii. To study reactions of *cis*-stilbene oxide **1i** with various anilines **9** by using the Sc/**L6**, In/**L6** and Fe/**L6** catalytic systems.

4. Results and Discussion

In our recent work, we have reported a novel method for the preparation of an analogue of Bolm's ligand **L6** (Figure 4).[28] We showed that our ligand **L6** proved its effectiveness and robustness in comparison with ligand **L3** in most cases. We obtained a very promising result in the case of ring-opening reaction of *meso*-stilbene oxide. The reaction of epoxide **1i** with 4-methoxybenzyl alcohol **8b** catalyzed by a Sc/**L6** catalytic system afforded corresponding product **9ib** in 82% yield with excellent 98% ee (Scheme 16).

Scheme 16: Alcoholysis of epoxide **1i**.[28]

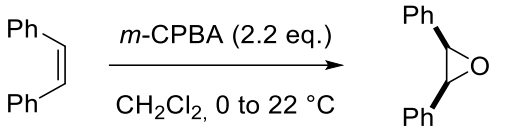


1i **8b** (2 eq.) **9ib**, 82%, 98% ee

4.1. Preparation of starting materials

Therefore, *cis*-stilbene oxide **1i** was chosen as a model substrate for extending the study of ring-opening reaction of *meso*-epoxides. It was prepared by a standard method: *cis*-stilbene **31** was treated with *m*-CPBA yielding epoxide **1i** in the range 78-83% yields (Scheme 17).[18]

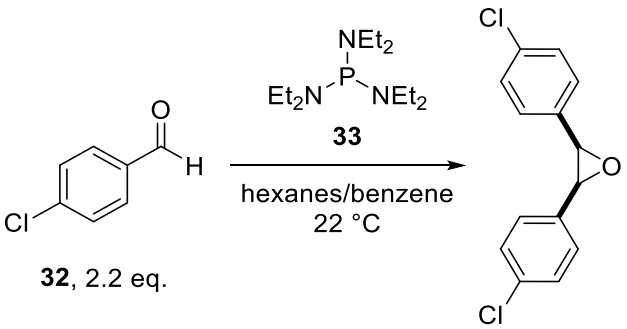
Scheme 17: Epoxidation of *cis*-stilbene **31**.



31 **1i**, 78-83%

Next, the chlorinated epoxide **1p** was prepared from 4-chlorobenzaldehyde **32** by using hexaethylphosphorous triamide **33** according to the reported procedure (Scheme 18).[20] The isolated yield was only 19% due to the incomplete conversion of starting material. Another reason for the low yield is that the reaction is not stereospecific and the *trans* isomer is formed as well. Both stereoisomers were separated by column chromatography.

Scheme 18: Formation of epoxide **1p**.

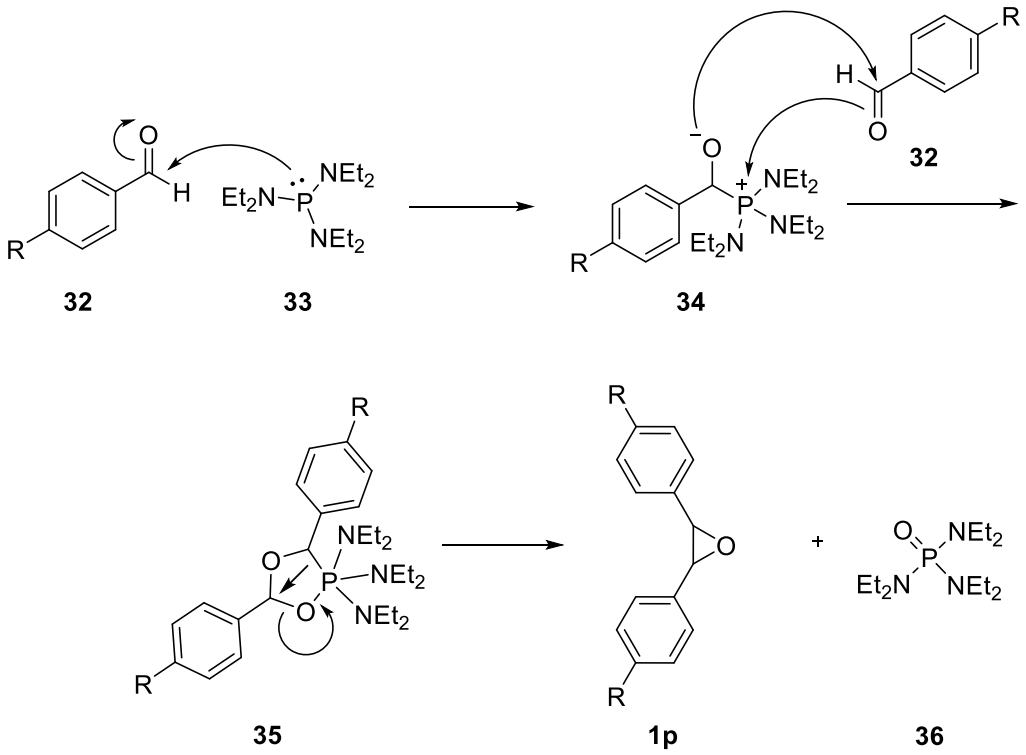


32, 2.2 eq. **1p**, 19%

In the same vein, I wanted to prepare an epoxide with electron donating substituents. Unfortunately, neither 4-methoxybenzaldehyde **39** nor 4-methylbenzaledehyde reacted at all under above mentioned conditions. The reason could be found in the proposed mechanism (Scheme 19). In the first step, the phosphorus lone pair attacks the carbonyl carbon resulting in a formation of an intermediate **34**. The possible explanation of unsuccessful formation of epoxide product from 4-methoxy or 4-methylbenzaldehyde is the electron-donating nature of these

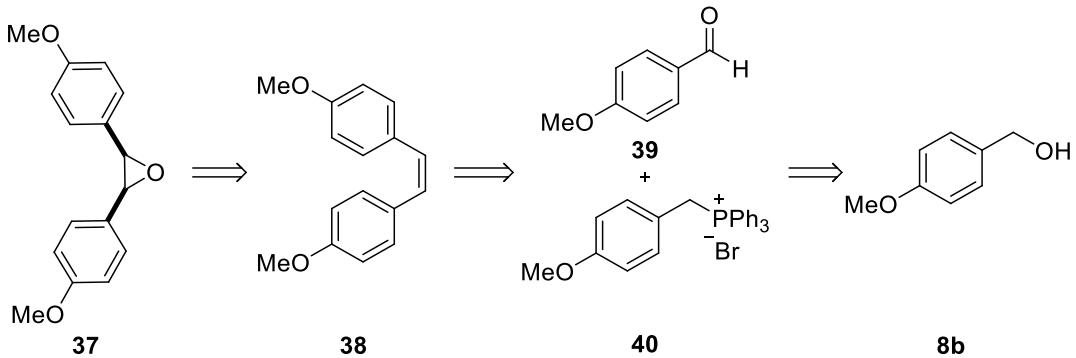
substituents, which are destabilizing intermediate **34**. Next, intermediate **35** is formed resulting in a production of an epoxide **1p** and hexaethylphosphoramide **36**.

Scheme 19: Proposed mechanism of a formation epoxide **1p**.



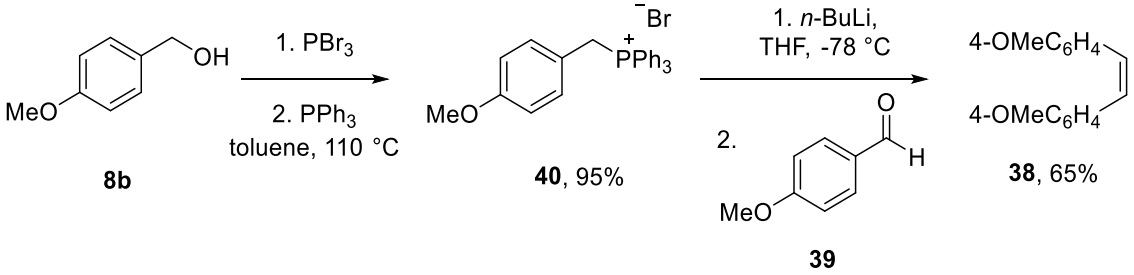
The next possible preparation protocol that I considered was to oxidize olefin **38** (Scheme 20). Further, the *cis*-olefin **38** can be synthesized from the aldehyde **39** and phosphonium bromide **40** under Wittig conditions. Last but not least, the phosphonium bromide **40** can be easily prepared from the corresponding alcohol **8b**.

Scheme 20: Retrosynthetic analysis of an epoxide **37**.



Following the retrosynthetic analysis, the alcohol **8b** was treated with phosphorus tribromide followed by the addition of triphenyl phosphine, which gave rise to the Wittig salt **40** in 95% isolated yield (Scheme 21). Next, the Wittig salt **40** was treated with *n*-butyllithium in THF at -78 °C. This was followed by the addition of 4-methoxybenzaldehyde **39** to afford the desired *cis*-olefin **38** in 65% isolated yield.

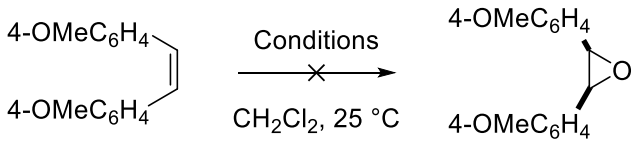
Scheme 21: Synthesis of olefin **38**.



8b **40**, 95% **39** **38**, 65%

The very first idea was to carry out the epoxidation under standard conditions with 2.2 equivalents of *m*-CPBA (Table 11, Entry 1). Unexpectedly, I observed formation of a complex mixture. I assumed that it was caused by the use an excess of the carboxylic peracid. Therefore, in the second attempt, I carried out the reaction with a lower amount of the peracid. The reaction again gave unsatisfactory result (Entry 2). Next, I presumed that sodium hydrogen carbonate could neutralize the carboxylic acid (by-product from the peracid) which probably caused the decomposition of the product (Entry 3). Even that did not help and despite all my efforts I was unable to synthesize the desired 4-methoxy substituted epoxide **37**.

Table 11: Attempts to synthesize of epoxide **37**.



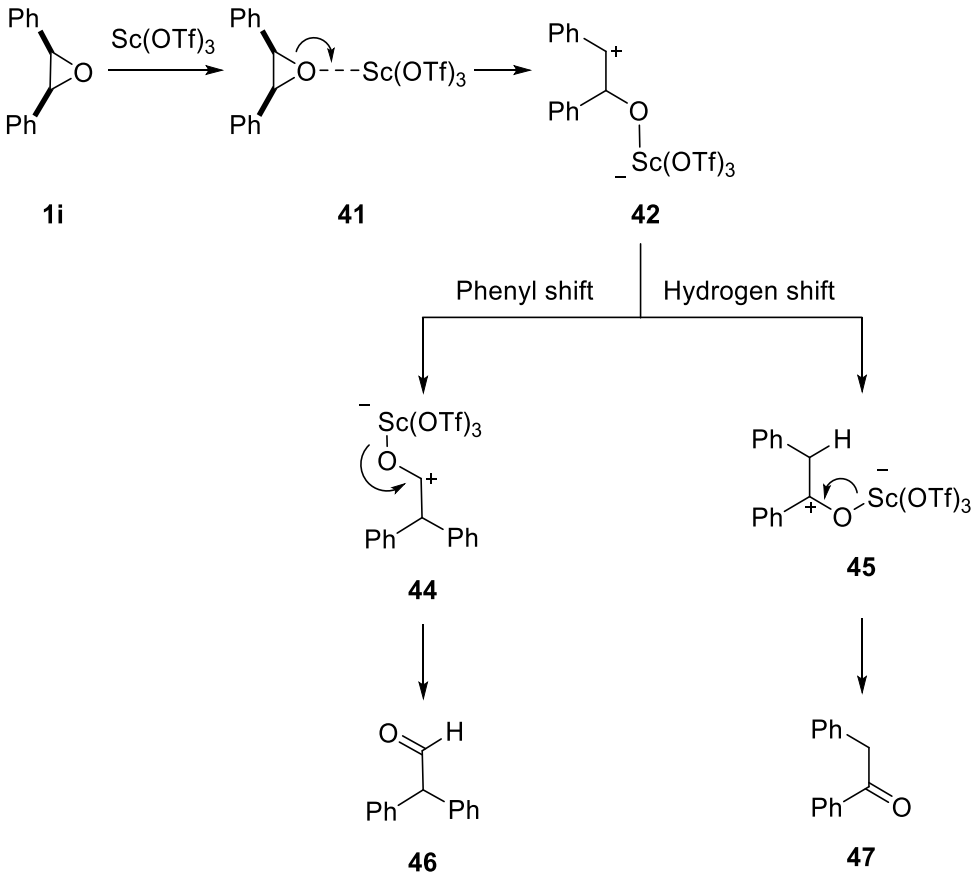
38 **37**

Entry	*m*-CPBA (eq.)	$NaHCO_3$ (eq.)	Yield (%)
1	2.2	-	Complex mixture
2	1.2	-	Complex mixture
3	1.2	1.2	Complex mixture

4.2. Ring-opening of *cis*-stilbene oxide with alcohols

During my bachelor's studies, I did the optimization of the catalytic system loading in model reaction (Scheme 16).[60] The enantioselectivity of the product **9ib** was still excellent (96%) even with 1 mol% catalytic system loading, but in expense of the reaction time (5 days). Therefore, from the practical point of view, I decided to carry out the reactions with 2 mol% catalytic system loading (enantioselectivity of **9ib** remained the same as with 10 mol% catalytic system loading). I also discovered that it is important to dry $Sc(OTf)_3$ and to distil alcohols prior to use in order to suppress formation of the undesired aldehyde **46** and ketone **47**. The formation of the aldehyde **46** and ketone **47** is induced by $Sc(OTf)_3$ (Scheme 22).[61] Once the $Sc(OTf)_3$ is coordinated to the epoxide's oxygen (intermediate **41**), the ring can be opened affording carbocation **42**. Consequently, the aldehyde **46** is formed after phenyl shift and ketone **47** after hydrogen shift, respectively.

Scheme 22: Formation of **46** and **47**.



In this work, I was pleased to obtain successful results which will be discussed hereinafter (Scheme 23). The reaction with 3-methoxybenzyl alcohol **8f** gave rise to product **9if** in 86% isolated yield with 98% ee. On the other hand, in the case of 2-methoxy derivative **8g**, a decrease of the enantioselectivity was observed (76%, 88% ee). The drop of enantioselectivity can be ascribed to the steric hindrance of the methoxy group in the *ortho*-position. A good result was also obtained with methyl substituted alcohol **8h** giving product **9ih** in 88% isolated yield with 98% ee. Reaction with benzyl alcohol **8i** proceeded smoothly and I isolated product **9ii** in 88% yield with excellent 98% ee. Satisfyingly, reactions with alcohols bearing electron withdrawing substituted groups such as bromo **8j**, carboxymethyl **8k**, nitro **8l** and trifluoromethyl **8m** afforded corresponding products **9ij** (78%, 93% ee), **9ik** (76%, 95% ee), **9il** (75%, 98% ee) and **9im** (86%, 98% ee).

Furthermore, different aromatic alcohols like 1-naphthylmethanol **8n** and 9-anthrylmethanol **8o** were studied. Product **9in** was obtained in 88% isolated yield in the reaction of epoxide **1i** with **8n** with excellent enantioselectivity (97% ee). Reaction with sterically hindered 9-antrylmethanol **8o** furnished product **9io** in 55% isolated yield with 95% ee. Worth mentioning is the fact that the reaction was not finished after eleven days and according to the ^{1}H NMR 30% of the starting epoxide **1i** was present in the reaction mixture. Presumably, the observed lower reactivity of the alcohol **8o** could be ascribed to the steric hindrance of the benzene rings and overall poor solubility. Therefore, I decided to carry out the reaction at 40 °C in order to speed up the reaction. The reaction then proceeded in 3 days delivering product **9io** in 63% isolated yield with even higher enantioselectivity (96% ee).

Gratifyingly, with heteroaromatic alcohols, furfuryl alcohol **8p** and thiophenemethanol **8q**, the reactions proceeded with excellent enantioselectivities, as well. However, in the first attempt with alcohol **8p** the reaction provided product **9ip** in 61% isolated yield with 85% ee and again the previously mentioned aldehyde **46** and ketone **47** were formed (combined ^{1}H NMR yield was 20%). The alcohol **8p** was used as purchased. So, I envisioned that one possible option how to avoid formation of those side products was to carry out the reaction with molecular sieves. I presumed that the molecular sieves are able to absorb the residual water in the reaction mixture. And indeed, the reaction with molecular sieves provided the product **9ip** in 75% ^{1}H NMR yield with 97% ee. However, according to the ^{1}H NMR there was still 25% of the starting epoxide **1i** even after 23 days. Reaction with alcohol **8q** proceeded smoothly delivering product **9iq** in 85% isolated yield with 97% ee.

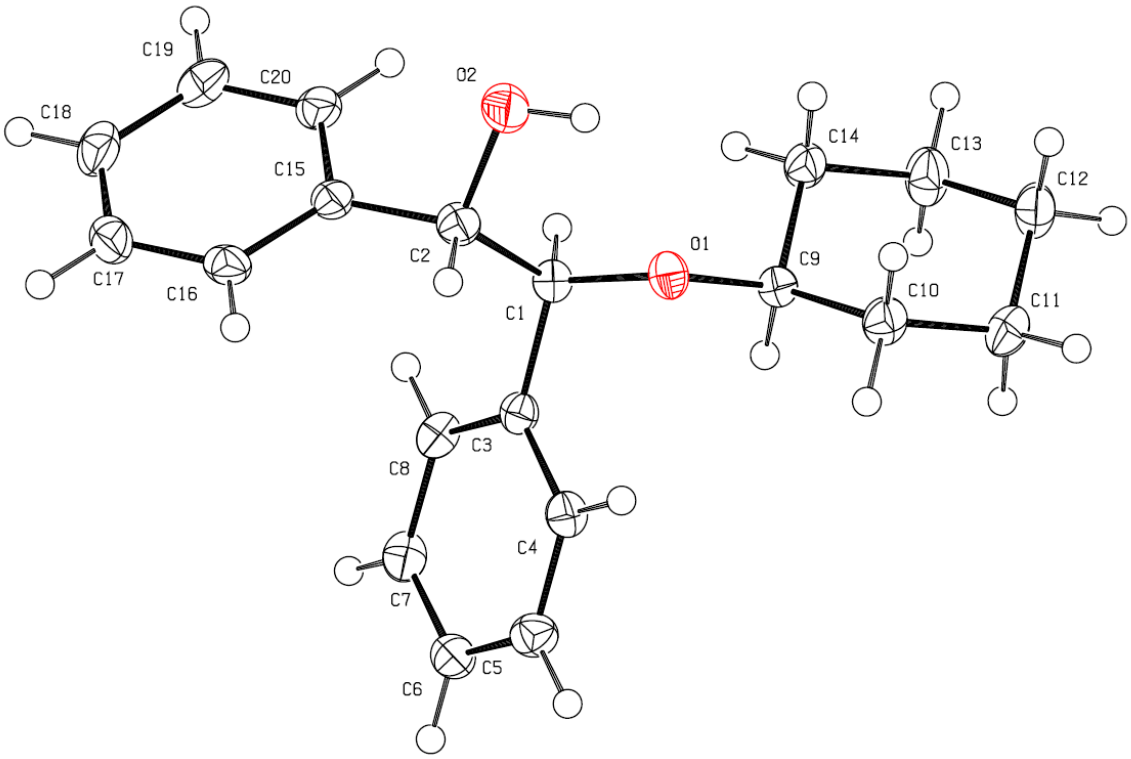
Reaction with ferrocene methanol **8r** furnished the product **9ir** in very low yield (27%) with 88% ee even after 11 days.

I want to emphasize that high enantioselectivities were also obtained with the aliphatic alcohols. The reaction of epoxide **1i** with methanol **8c** and allyl alcohol **8d** proceeded smoothly providing products **9ic** and **9id** in very good yields (87 and 86%) and with high enantioselectivities (93 and 95% ee).

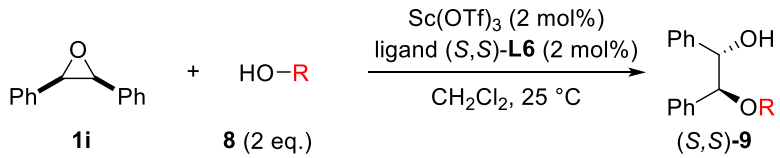
Moreover, I performed a reaction of epoxide **1i** with propargyl alcohol **8e** (fractionally distilled prior to use), however, it provided product **9ie** in 70% ^{1}H NMR yield along with aldehyde **46** and ketone **47** (combined ^{1}H NMR yield was 15%). I, therefore, undertook a more meticulous drying procedure of propargyl alcohol **8e**. It was first dried over potassium carbonate, fractionally distilled and then dried over the molecular sieves overnight. Only after that particular drying procedure I was delighted to report a formation of the product **9ie** in 81% isolated yield (no side products) with excellent 98% ee.

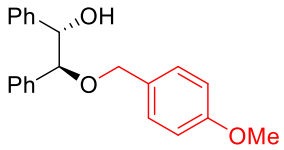
Last but not least, I made an effort to carry out a reaction of epoxide **1i** with cyclohexanol **8s**. Having in mind that **8s** is quite hygroscopic, I decided in the very first attempt to apply the above-mentioned drying procedure. I dried **8s** over potassium carbonate, distilled it fractionally and dried over molecular sieves overnight. Nonetheless, the product **9is** was obtained in 70% ^{1}H NMR yield with 86% ee along with aldehyde **46** and ketone **47** (combined ^{1}H NMR yield was 15%). On the assumption that in the reaction with furfuryl alcohol **8p** I overcame the formation of the side products using molecular sieves as an additive. I decided to carry out reaction with alcohols **8s** with molecular sieves, as well. As expected, I was delighted to obtain **9is** in 83% isolated yield with the excellent 99% ee. The structure of the product **9is** was confirmed by a single crystal X-ray analysis (Figure 12).

Figure 12: The X-ray structure of (*S*,*S*)-**9is**. Ellipsoids are shown with 30% probability.

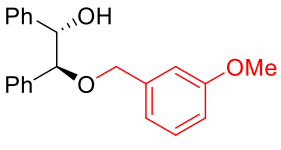


Scheme 23: Ring-opening of *cis*-stilbene oxide **1i** with alcohols **8**

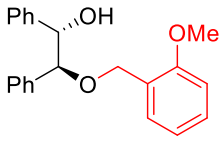




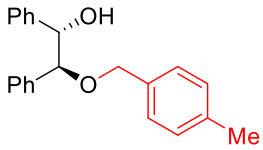
9ib, 82%,[1] 68 h
98% ee



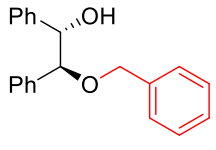
9if, 86%,[1] 156 h
98% ee



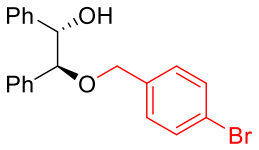
9ig, 76%,[1] 116 h
88% ee



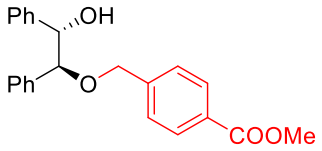
9ih, 88%,[1] 72 h
98% ee



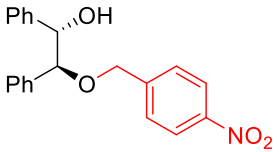
9ii, 88%,[1] 91 h
98% ee



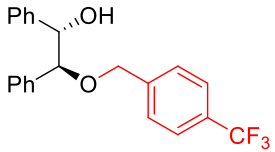
9ij, 78%,[1] 69 h
93% ee



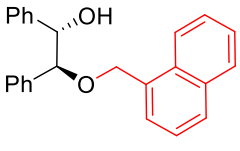
9ik, 76%,[1] 86 h
95% ee



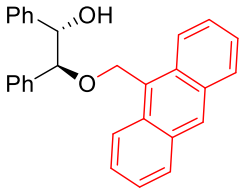
9il, 75%,[1] 69 h
98% ee



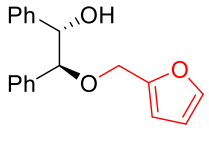
9im, 86%,[1] 116 h
98% ee



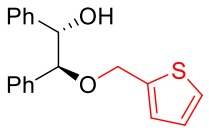
9in, 88%,[1] 107 h
97% ee



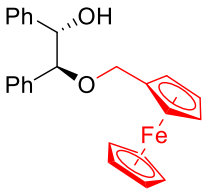
9io, 55%,[2] 11 d, 95% ee
63%,[1] 72 h[2], 96% ee



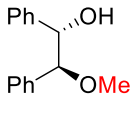
9ip, 61%,[1] 69 h, 85% ee
75%,[2] 23 d[3], 97% ee



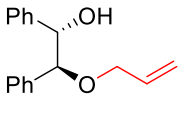
9iq, 85%,[1] 114 h
97% ee



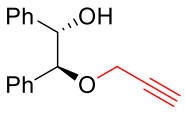
9ir, 27%,[1] 11 d
89% ee



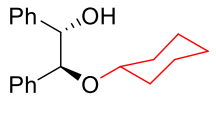
9ic, 87%,[1] 86 h
93% ee



9id, 86%,[1] 86 h
95% ee



9ie, 81%,[1] 96 h
98% ee



9is, 59%,[2] 70 h,[4] 86% ee
83%,[1] 23 d,[5] 99% ee

[1] Isolated yield. [2] ^{1}H NMR yield. [3] 40 °C. [4] With 4Å MS (25% of **1i**). [5] Cyclohexanol was distilled. [6] Cyclohexanol was dried over K_2CO_3, distilled and stored over 3Å MS.

4.3. Influence of the catalytic system and reaction conditions on the selectivity of the reaction

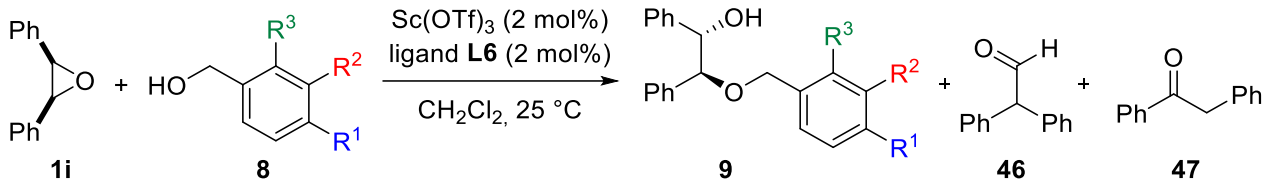
In this chapter, the influence of the redried $Sc(OTf)_3$ on the selectivity of the reaction will be discussed. I found that before each reaction a fresh batch of $Sc(OTf)_3$ had to be used. Reactions carried out using this drying procedure led to the results mentioned in Scheme 23 and also placed in Table 17 for a reference (Entries 1, 3, 6, 9 and 12). On the other hand, the repetitive use of $Sc(OTf)_3$ resulted in lower enantioselectivity along with the formation of aldehyde **46** and ketone **47**.

A reaction of epoxide **1i** with alcohol **8b** using redried $Sc(OTf)_3$ afforded **9ib** in just 50% ^{1}H NMR yield with 70% ee along with aldehyde **46** and ketone **47** in 25% and 6% ^{1}H NMR yields, respectively (Table 12, Entry 2). I also performed reactions of **1i** with **8f**, **8g**, **8l** and **8m** with redried $Sc(OTf)_3$. Each reaction provided the respective products **9if** (46% ^{1}H NMR yield, 62% ee, Entry 4), **9ig** (42% ^{1}H NMR yield, 45% ee, Entry 7), **9il** (40% ^{1}H NMR yield, 81% ee, Entry 10) and **9im** (35% ^{1}H NMR yield, 56% ee, Entry 13) in both lower yields and enantioselectivities along with formation of the side products **46** and **47**. Obviously, the results with redried $Sc(OTf)_3$ are not satisfactory.

Nonetheless, I carried out the reactions with 10 equivalents of the benzyl alcohols as I assumed that it could suppress the formation of the aldehyde **46** and ketone **47** with redried $Sc(OTf)_3$. An increased amount of alcohol could shift the balance in favor of the product formation. To my delight, I observed that it not only suppressed formation of aldehyde **46** and ketone **47**, but also increased the enantioselectivity of the desired products. In the reaction with **8f** the respective **9if** was formed in 74% isolated yield with 83% ee (Entry 5). The reaction time was up to 6 days and the undesired aldehyde **46** was still formed (5% ^{1}H NMR yield). In the reaction with **8g,** product **9ig** was formed in 50% isolated yield, but in just 24% ee (Entry 8). Regarding the reaction with **8f**, it provided **9if** in 48% isolated yield with 92% ee (Entry 11). Then, I carried out the reaction with **8m**. In this case, I was also able to partially suppress formation of the aldehyde **46** and ketone **47**, but regrettably the enantioselectivity of the product **9im** formed in 53% yield was reduced to 37% ee (Entry 14).

To sum it up, I found that increasing the amount of the alcohols can suppress the formation of the aldehyde **46** and ketone **47**.

Table 12: Alcoholysis of *cis*-stilbene oxide **1i** with various benzyl alcohols **8**.



1i **8** **9** **46** **47**

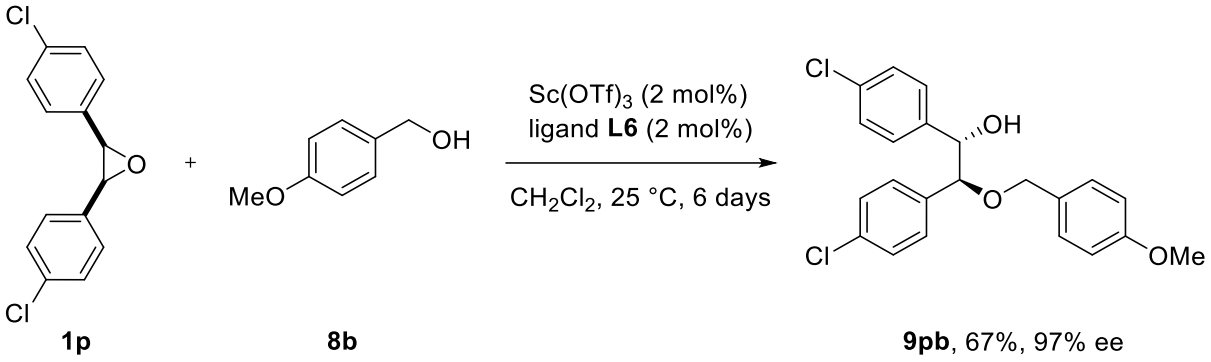
Entry	Alcohol **8**	R^1	R^2	R^3	**8** (eq.)	t (h)	**9**	Yield (%)[a]	ee (%)	**46** (%)	**47** (%)	Notes
1[b]	**8b**	OMe	H	H	2	68	**9ib**	82 (90)	98	ND	ND	
2[c]	**8b**	OMe	H	H	2	68	**9ib**	ND (50)	70	25	6	
3[b]	**8f**	H	OMe	H	2	156	**9if**	86	98	ND	ND	
4[c]	**8f**	H	OMe	H	2	39	**9if**	42 (46)	62	25	6	
5[c]	**8f**	H	OMe	H	10	141	**9if**	74 (80)	83	5	1	
6[b]	**8g**	H	H	OMe	2	116	**9ig**	76	88	ND	ND	
7[c]	**8g**	H	H	OMe	2	90	**9ig**	ND (42)	45	20	8	
8[c]	**8g**	H	H	OMe	10	41	**9ig**	50 (60)	24	16	4	
9[b]	**8l**	NO_2	H	H	2	69	**9il**	75	98	ND	ND	
10[c]	**8l**	NO_2	H	H	2	24	**9il**	41 (40)[d]	81	35	ND	*syn*-**9il**, 13%
11[c]	**8l**	NO_2	H	H	10	17	**9il**	48 (55)	92	16	4	*syn*-**9il**, 3%
12[b]	**8m**	CF_3	H	H	2	116	**9im**	86	98	ND	ND	
13[c]	**8m**	CF_3	H	H	2	41	**9im**	ND (35)[d]	56	42	12	*syn*-**9im**, 9%
14[c]	**8m**	CF_3	H	H	10	20	**9im**	53 (50)[d]	37	23	8	*syn*-**3im**, 9%

[a] Isolated yields, ^{1}H NMR yields in parenthesis. [b] Model reaction. $Sc(OTf)_3$ was dried before the reaction (Scheme 23). [c] The reaction was catalyzed by redried $Sc(OTf)_3$ that was previously dried after taken from a flask. [d] Also *syn* is formed. Isolated yield of *syn* and *anti* isomers **3**.

4.4. Ring-opening of substituted *cis*-stilbene oxide with alcohol 8b

I also examined the ring-opening of *cis*-bis(4-chlorophenyl)oxirane **1p** with 4-methoxybenzyl alcohol **8b** catalyzed by the catalytic system Sc/**L6** (Scheme 24). The reaction delivered product **9pb** in 67% isolated yield with the excellent 97% ee.

Scheme 24: Alcoholysis of epoxide **1p**.

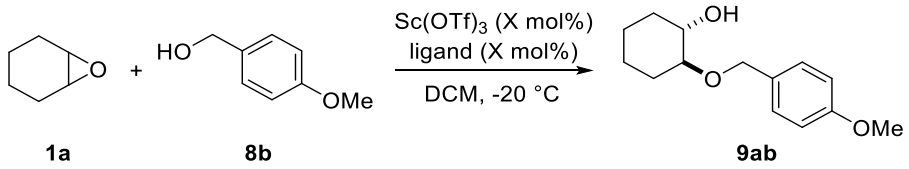


1p **8b** **9pb**, 67%, 97% ee

4.5. Ring-opening of aliphatic epoxides with alcohols

First, I decided to perform the reaction of cyclohexene oxide **1a** with 4-methoxybenzyl alcohol **8b** under conditions reported by Schneider *et al.* (Table 14, Entry 1).[17] So, the reaction with Sc/**L3** with 10 mol% catalytic system loading provided the product **9ab** in 75% ^{1}H NMR yield with 34% ee (Entry 2). The other reaction with Sc/**L6** with 2 mol% catalytic system loading provided a product **9ab** in 70% ^{1}H NMR yield with 33% ee (Entry 3). In both cases, the obtained enantioselectivities of the product **9ab** are lower (Entries 2 and 3) than the one reported by Schneider *et al.* (Entry 1). Interestingly, when I carried out the reaction with the Sc/**L6** at 30 °C, I obtained the product **9ab** in a similar ^{1}H NMR yield (80%), but with a higher enantioselectivity (42% ee, Entry 4) in comparison to the previous attempts.

Table 13: Alcoholysis of epoxide **1a** with alcohol **8b**.



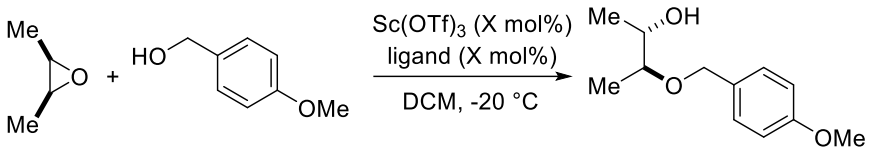
1a **8b** **9ab**

Entry	$Sc(OTf)_3$ (mol %)	Ligand (mol%)	Time (days)	^{1}H NMR yield (%)	ee (%)[b]
1[17]	10	(*R*,*R*)-**L3** (10)	1	90[a]	54 (*R*,*R*)
2	10	(*S*,*S*)-**L3** (10)	1	75	34 (*S*,*S*)
3	2	(*S*,*S*)-**L6** (2)	3	70	33 (*S*,*S*)
4[b]	10	(*S*,*S*)-**L6** (10)	1	80	42 (*S*,*S*)

[a] Isolated yield. [b] The reaction was carried out at 30 °C.

I also decided to perform the reaction of epoxide **1d** with alcohol **8b** under condition reported by Schneider *et al.* (Table 14, Entry 1).[17] The reaction with Sc/**L3** with 10 mol% catalytic system loading provided the product **9db** in 25% ^{1}H NMR yield with 53% ee (Entry 2). The other reaction with Sc/**L6** with 2 mol% catalytic system loading provided a product **9db** in 40% ^{1}H NMR yield with 52% ee (Entry 3). In both cases, the obtained enantioselectivities of the product **9db** are similar (Entries 2 and 3) to the one reported by Schneider *et al.* (Entry 1). Interestingly, when I carried out the reaction with the Sc/**L6** at 30 °C, I obtained **9db** in 63% ^{1}H NMR yield, but with a lower enantioselectivity (43%, Entry 4) in comparison to the previous attempts.

Table 14: Alcoholysis of epoxide **1d** with alcohol **8b**.



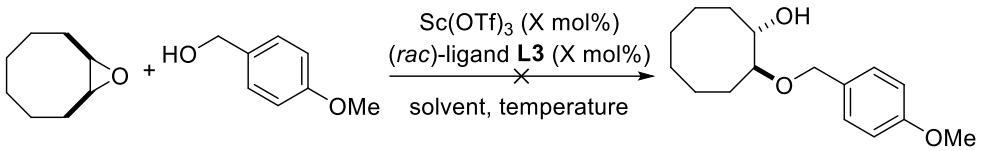
1d **8b** **9db**

Entry	$Sc(OTf)_3$ (mol%)	Ligand (mol%)	Time (days)	^{1}H NMR Yield (%)	ee (%)
1[17]	10	(*R,R*)-**L3** (10)	1	93[a]	49 (*R,R*)
2	10	(*S,S*)-**L3** (10)	1	25	53 (*S,S*)
3	2	(*S,S*)-**L6** (2)	3	40	52 (*S,S*)
4[b]	10	(*S,S*)-**L6** (10)	1	63	43 (*S,S*)

[a] Isolated yield. [b] The reaction was carried out at 30 °C.

I wanted to accomplish the reaction of *cis*-cyclooctene oxide **1w** with 4-methoxybenzyl alcohol **8b** (Table 15). I want to point out that the reason why I performed this reaction is based on Malkov *et al*. work.[57] They described a correlation between the size of the cycle of the epoxide and the enantioselectivity of the ring-opened product. The bigger the cycle is the higher the enantioselectivity. In the first attempt, I carried out the reaction under my standard reaction conditions, but without any success (Entry 1). Neither the increase of catalytic system loading to 10 mol% (Entry 2) nor the increase of temperature from 25 to 40 °C (Entry 3) provided **9wb**. When I further increased the reaction temperature, I had to change the solvent from dichloromethane to dichloroethane. Even in this case the reaction did not proceed to deliver the desired product **9wb** (Entry 4). Nonetheless, I observed formation of a side product by the ^{1}H NMR as well as TLC analysis. I isolated the side product in a sufficient amount for its analysis. I consider a possible formation of an ether functional group for the reason that the chemical shift at 4.45 (red line in Figure 13) is typical for ethers. However, the ether had to be formed from the alcohol **8b**, because epoxide **1w** did not react (no conversion). I deduced that the side product could be ether **45**. I measured the high resolution mass spectrum of the side product **45** to prove this. The result of the analysis confirms the proposed structure. Unfortunately, I was unable to determine the mechanism of the formation of the side product **45**. In conclusion, I envisioned that the replacement of 4-methoxybenzyl alcohol **8b** by some more reactive alcohol, such as methanol **8c**, could be a better choice.

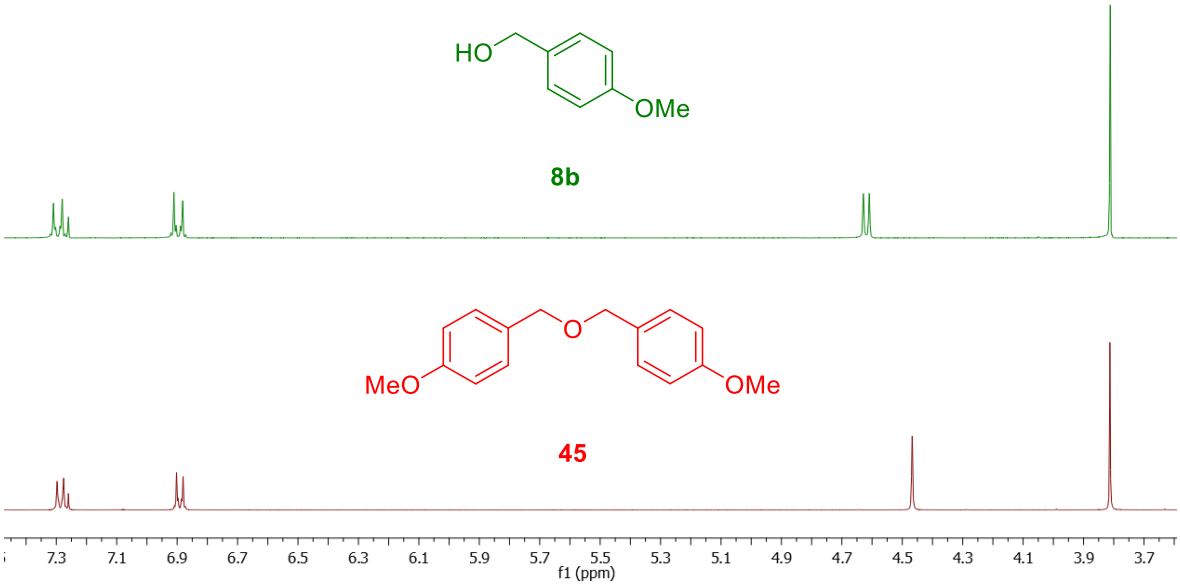
Table 15: Attempts to synthesize a product **9wb**.



1w **8b** **9wb**

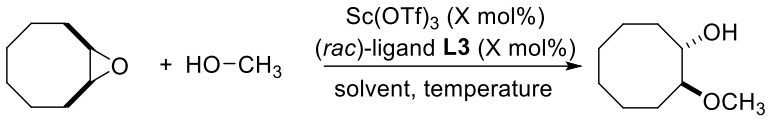
Entry	Catalyst (mol %)	Solvent	Temperature (°C)	^{1}H NMR yield (%)	Conversion (%)
1	2	CH_2Cl_2	25	0	0
2	10	CH_2Cl_2	25	0	0
3	10	CH_2Cl_2	40	0	0
4	10	$Cl(CH_2)_2Cl$	70	0	0

Figure 13: ^{1}H NMR spectrum of the alcohol **8b** (green) and side product **45** (red).



Regrettably, neither reaction of epoxide **1w** with methanol **8c** at 25 °C (Table 16 ,Entry 1), nor at 40 °C (Entry 2), nor at 70 °C (Entry 3) gave rise to **9wc**. Moreover, at 70 °C the formation of a complex reaction mixture was observed. There still remained a possibility to conduct the reaction in methanol itself. The reaction at 25 °C did not proceed (Entry 4) yet running the reaction at 70 °C finally provided the desired product **9wc** in quantitative yield (Entry 5).

Table 16: Attempts to synthesize the product **9wc**.

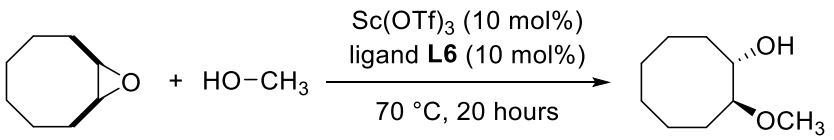


1w **8c** **9wc**

Entry	Catalyst (mol %)	Solvent	Temperature (°C)	^{1}H NMR yield (%)
1	10	CH_2Cl_2	25	0
2	10	CH_2Cl_2	40	0
3	10	$Cl(CH_2)_2Cl$	70	0
4	10	-	25	0
5	10	-	70	>96

Having the optimal conditions established, I carried out the reaction of *cis*-cyclooctene oxide **1w** with neat methanol **8c** with Sc/**L6** catalytic system (Scheme 25). I was delighted to isolated product **9wc** in 85% isolated yield. Unfortunately, another problem occurred in attempt to determine the enantioselectivity of the product by HPLC. I was unable to separate the product **9wc** on any available chiral stationary phase. Fortunately, **9wc** contains a hydroxyl group, which make it possible to react with a Mosher's acyl chloride reagent to form the corresponding diastereoisomeric Mosher esters. The Mosher esters would have two distinguishable signals in ^{19}F NMR spectrum. By integrating the respective signals, it is possible to determine the ratio between the diastereoisomeric Mosher esters. I obtained Mosher esters from product **9wc** in quantitative yield with ratio 2/98.

Scheme 25: Alcoholysis of the epoxide **1w**.



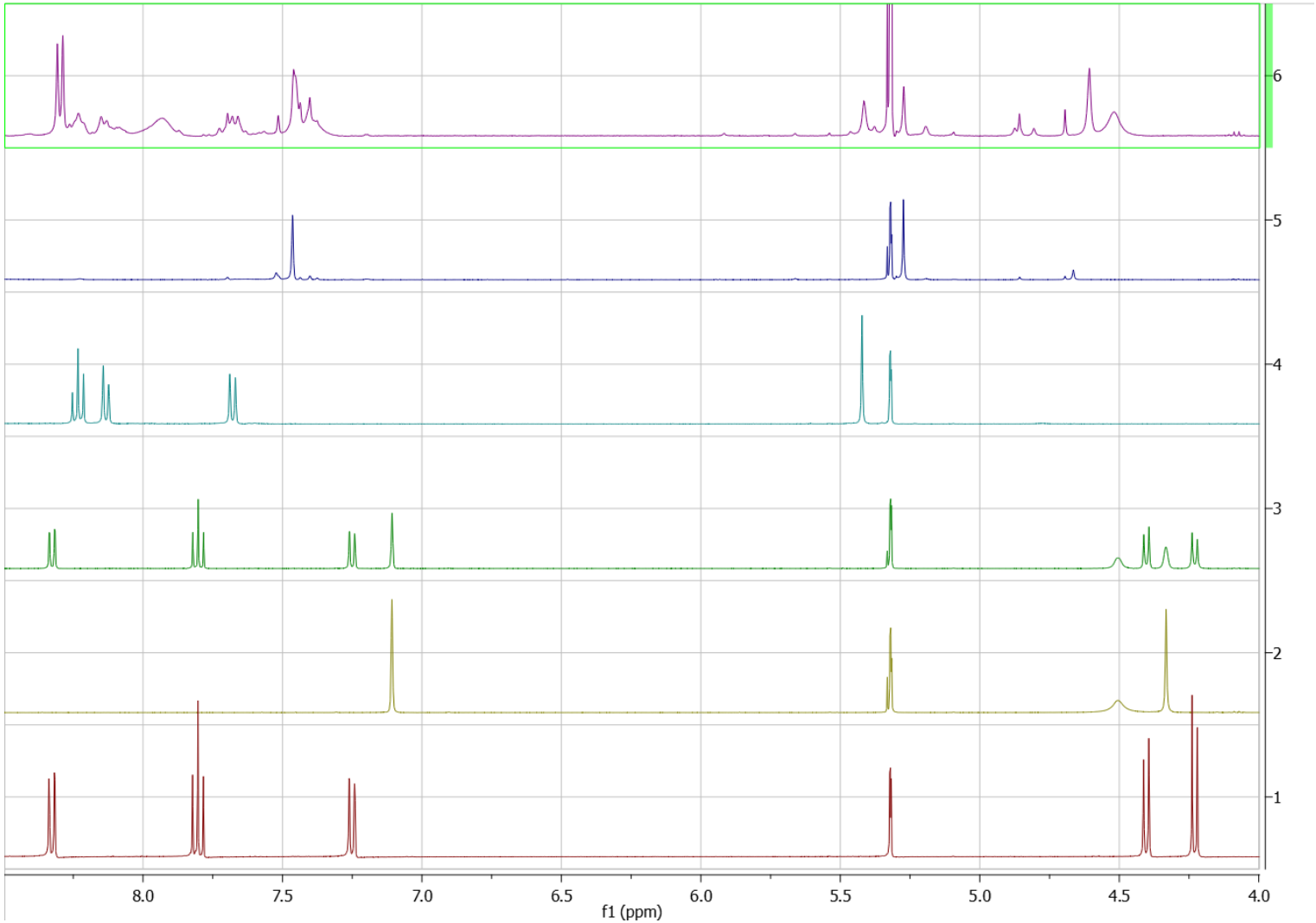
1w **8c** (excess) **9wc**, 85%, 96% ee

4.6. Study of the catalytic complex

I also tried to study the Sc/**L6** catalytic system to shed some light on the structure of the complex. I have discussed in the section 2.1.2 that Schneider *et al.* reported a X-ray structure of the Sc/**L3** complex (Figure 2).[21] The X-ray analysis showed that the complex contains a single ligand molecule having nitrogen atoms coordinated to the metal ion. However, in the case of a Sc/**L6** complex this would be possible with difficulties. The cyclopentane rings would not allow the pyridine rings to take on a coplanar conformation. This could lead to a formation of complexes possessing multiple metal centers (higher aggregates). This was observed previously by my colleagues.[28] . Despite all the effort, I did not succeed in growing crystals suitable for X-ray diffraction analysis. Therefore, I tried to record the ^{1}H NMR spectrum of the Sc/**L6** complex and compared it with spectrum of the Sc/**L3** (Figure 14). The ^{1}H NMR spectrum of the Sc/**L3** (turquoise line) clearly indicates the formation of a single structure from $Sc(OTf)_3$ and **L3** (red line). On the other hand, mixing $Sc(OTf)_3$ with **L6** (yellow line) formed obviously not a single structure as it is indicated by the presence of more than one signal in the aromatic area (blue line). Next, I assumed that I could test the competitive complexation of ligands **L3** and **L6** with $Sc(OTf)_3$ to see if one of them could coordinate preferentially. Accordingly, I mixed together $Sc(OTf)_3$, ligands **L3** and **L6** in the ratio 1:1:1 for 10 minutes and measured the ^{1}H NMR spectrum (purple). The analysis revealed that probably both complexes are formed, considering corresponding signals at 5.47 (**L3**) and 5.29 (**L6**).

Furthermore, I decided to measure the mass spectrum of the complex $Sc(OTf)_3$ with **L6** (900.44 m/z) in acetonitrile. One of the peaks (751.26 m/z) [M – OTf^-] indicates the presence of $Sc^+(OTf)_2$-**L6**. Unfortunately, the other signals did not support the assumption of the presence of some higher aggregates. However, when I carried out the model reaction: *cis*-stilbene oxide **1i** with alcohols **8b** in acetonitrile, the reaction provided product **9ib** in just 16% ^{1}H NMR yield along with 4% aldehyde **46** after 5 days as a racemic mixture (69% of the **1i** remained unreacted). This result clearly pointed out that acetonitrile is not a suitable medium for complexation studies. Detailed analysis of the catalytic system is still ongoing.

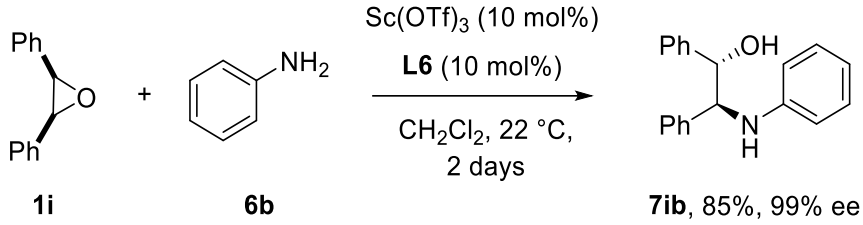
Figure 14: ^{1}H NMR in CD_2Cl_2 of ligand **L3** (red), **L6** (yellow), **L3** and **L6** (green), Sc/**L3** (turquoise), Sc/**L6** (blue) and Sc/**L3**+**L6** (purple).



4.7. Ring-opening of *cis*-stilbene oxide with amines

During my previous study, the reaction of *cis*-stilbene oxide **1i** with aniline **6b** catalyzed by the Sc/**L6** catalytic system (Figure 4) afforded the corresponding product **7ib** in 85% isolated yield with the excellent 99% ee (Scheme 26).[28] Hence, encouraged by this result, I decided to extend the scope of the reaction with a respect to different amines **6**.

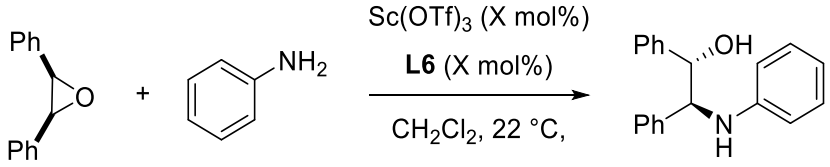
Scheme 26: Aminolysis of *cis*-stilbene oxide **1i** with aniline **6b**.



1i **6b** **7ib**, 85%, 99% ee

First regarding this chapter, I carried out a study of the effect of catalyst loading on the enantioselectivity (Table 17). A decrease of the catalyst loading to 5 mol% gave desired product **7ib** in 72% ^{1}H NMR yield with 95% ee, but the reaction time increased to 4 days (Entry 2). Its further lowering to 2 mol% led to a much longer reaction time (8 days), but almost the same yield (76%) and enantioselectivity (93%) (Entry 3). Surprisingly, reaction using 1 mol% load furnished product **7ib** in just 34% ^{1}H NMR yield with 87% ee (Entry 4). From the practical point of view, I decided to carry the subsequent reactions with 5 mol% load.

Table 17: Effect of the catalyst loading on the enantioselectivity.

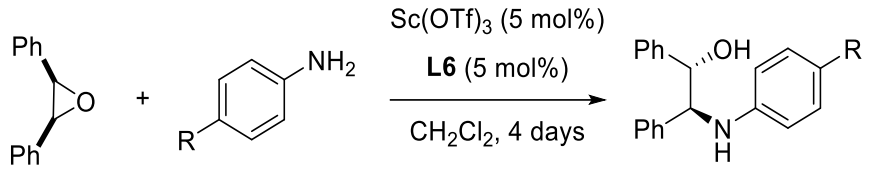


1i **6b** **7ib**

Entry	Catalyst (mol %)	Reaction time (days)	^{1}H NMR yield (%)	ee (%)
1	10	2	90	99
2	5	4	72	95
3	2	8	76	93
4	1	18	34	87

Furthermore, I decided to study the outcome of reactions with two different anilines bearing electron donating and withdrawing group, respectively (Table 18). The reaction with 4-methoxyaniline **6a** provided product **8ic** in 45% ^{1}H NMR yield and 86% ee (Entry 1). It is described in the literature that higher enantioselectivity was obtained by lowering the reaction temperature to 0 °C. By virtue of this, I performed the same reaction again at 0 °C, but the product **7ia** was obtained in lowered enantiopurity (68%) albeit the yield was higher (80%, Entry 2). On the other hand, the reaction with 4-chloroaniline **7c** provided product **7ic** in a lower yield (53%), although in the excellent enantioselectivity (97%, Entry 3).

Table 18: Aminolysis of the oxide **1i** with anilines **6a** and **6c**.



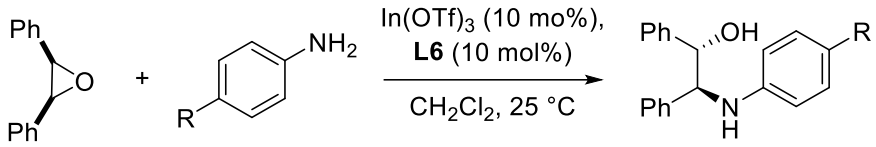
1i **6** **7**

Entry	Amine **6**	R	T (°C)	Product **7**	^{1}H NMR yield (%)	ee (%)
1	**6a**	OMe	25	**7ia**	45	86
2[a]	**6a**	OMe	0	**7ia**	80	68
3	**6c**	Cl	25	**7ic**	53	97

[a] Reaction carried out at 0 °C.

In addition, I performed reactions of *cis*-stilbene oxide **1i** with anilines **6a-c** under two different conditions reported by Schneider *et al.*[20] and Ollevier *et al.*[62], but using the ligand **L6** instead (Table 19). The first one by Schneider *et al.* required $In(OTf)_3$ (10 mol%) and 2 eq. of the corresponding aniline **6**. By using the first, the reaction with aniline **6b** delivered product **7ib** in 80% ^{1}H NMR yield and only 76% ee (Entry 1). The reaction of oxide **1i** with aniline **6a** provided **7ia** in 85% ^{1}H NMR yield and 71% ee (Entry 2). A good result was obtained with 4-chloroaniline **6c** giving **7ic** in 80% ^{1}H NMR yield and 91% ee (Entry 3).

Table 19: Aminolysis of oxide **1i** with anilines **6a-c** with In/**L6**.

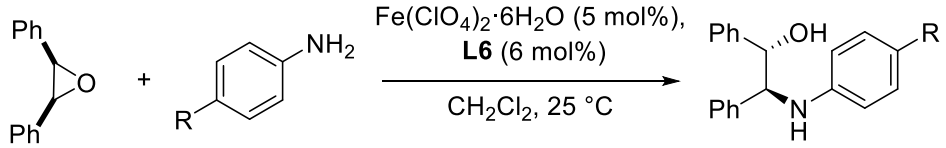


1i **6** (2 eq.) **7**

Entry	Amine **6**	R	Product **7**	^{1}H NMR yield (%)	ee (%)
1	**6b**	H	**7ib**	80	76
2	**6a**	OMe	**7ia**	85	71
3	**6c**	Cl	**7ic**	80	91

The second method (Olevier *et al.*) required the use of $Fe(ClO_4)_2 \cdot 6H_2O$ (5 mol%) (Table 20). The reaction with aniline **6b** yielded **7ib** in 55% ^{1}H NMR yield with 83% ee (Entry 1). Unfortunately, the reactions with anilines **6a** and **6c** did not proceed well. In both cases, the yields were very low (10% and 16%, respectively). The enantioselectivity of the product **7ia** was not determined due to the low yield and conversion (Entry 2). Enantiopurity of **7ic** was 65% ee (Entry 3).

Table 20: Aminolysis of oxide **1i** with anilines **6a-c** with Fe/**L6**.



1i **6** (1 eq.) **7**

Entry	Amine **6**	R	Product **7**	^{1}H NMR yield (%)	ee (%)
1	**6b**	H	**7ib**	55	83
2[a]	**6a**	OMe	**7ia**	10	ND
3	**6c**	Cl	**7ic**	16	65

[a] 80% of **1i** was still present in the reaction mixture. ND = not determined.

5. Experimental Part

5.1. General

All chemicals were purchased from common commercial sources – Sigma Aldrich, Fluorochem, Alfa Aesar, Acros Organics and PENTA. CH_2Cl_2 for reaction was purified and dried by distillation from CaH_2. Solvents (Hexanes, EtOAc, Et_2O) for column chromatography were distilled prior to use. Scandium(III) triflate was dried under reduced pressure at 130 °C prior to use. 4-Methoxy, 3-methoxy and 2-methoxybenzyl alcohols, benzyl alcohol and allyl alcohol were fractionally distilled prior to use. Propargyl alcohol and cyclohexanol were dried over K_2CO_3, fractionally distilled and dried over MS 3Å overnight. Methanol (HPLC) was dried over 3Å MS overnight. Ligands (*S*,*S*)-**L3** and (*S*,*S*)-**L6** were prepared in laboratory during a previous project.[28] Argon was used as a source of an inert atmosphere.

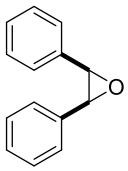
TLC was performed on aluminum sheets with layer of Silica gel 60 F_{254}, purchased from Merck. Spots on TLC were detected by using UV lamp (254 nm), solution of potassium permanganate and Hanessian's stain solution. Silica gel 60 (0.040 – 0.063 mm, Merck) was used for column chromatography.

NMR spectra were recorded on Bruker Avance III ($\nu(^1H)$ = 400 MHz, $\nu(^{13}C)$ = 100 MHz, $\nu(^{19}F)$ = 377 MHz) in deuterated chloroform, referenced to residual solvent peak (^1H: 7.26 ppm, ^{13}C: 77.16 ppm). Chemical shifts are given in δ-scale, coupling constants *J* are given in Hz. The following abbreviations were used to define the signal multiplicity: s – singlet, br s – broad singlet, d – doublet, t – triplet, dd – doublet of doublet, ddt – doublet of doublet of triplet, m – multiplet. 1,2,4,5–tetramethylbenzene was used as an internal standard.

Infrared spectra were measured in KBr on spectrometer Herno Nicolet AVATAR 370 FT-IR. Mass spectra were measured on spectrometer VG-Analytical ZAB-SEQ. All melting points are uncorrected and were determined on Bűchi Melting Point B-545. Optical rotations were measured on automatic polarimeter Autopol III and datas are shown in $deg \cdot mg^{-1} \cdot dm^{-1}$ with accuracy ± 2° and with mass concentration in g/100 mL. HPLC analyses were done on Schimadzu chromatograph with Daicel Chiralpack® columns.

5.2. Preparation of Starting Materials

cis-Stilbene oxide (1i)



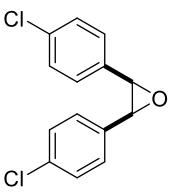
m-CPBA (3.2 g, 18 mmol) was added in small portions to a cooled solution of *cis*-stilbene **31** (1.5 mL, 8.2 mmol) in CH_2Cl_2 (100 mL) in a dry and argon flushed 250 mL flask. After 24 hours, the reaction mixture was diluted with saturated $NaHCO_3$ (50 mL) and extracted with Et_2O (3×30 mL). The combined organic phases were washed with brine (30 mL) and dried over $MgSO_4$. Column chromatography of the residue on silica gel (gradient hexanes/Et_2O from 40/1 to 20/1) furnished 1.3 g (83%) of the title compound as a colorless liquid, which solidified upon standing.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24–7.10 (m, 10H, Ar-H), 4.37 (s, 2H, CH).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 134.51, 127.92, 127.65, 127.01, 59.90.

The recorded values were in agreement with the published data.[27]

(2*R*,3*S*)-2,3-Bis(4-chlorophenyl)oxirane (1p)



Hexaethylphosphorous triamide **33** (2 mL, 7.5 mmol) in benzene:hexanes (1:1; 4 mL) was added dropwise to a cooled solution of 4-chlorobenzaldehyde **32** (2.5 g, 18.2 mmol) in benzene (1 mL) . After 2 days, the reaction mixture was quenched with water (75 mL) and extracted with CH_2Cl_2 (4×100 mL). The combined organic phases were dried over $MgSO_4$. Column chromatography of the residue on silica gel (gradient hexanes/DCM from 5/1 to 4/1) furnished 380 mg (19%) of the title compound as a colorless liquid, which solidified upon standing.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.22–7.17 (m, 4H, Ar-H), 7.13–7.08 (m, 4H, Ar-H), 4.33 (s, 2H, CH).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 133.74, 132.70, 128.35, 128.26, 59.28.

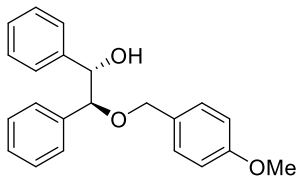
The recorded values were in agreement with the published data.[63]

5.3. Ring-Opening of *meso*-Epoxides with Alcohols

General procedure for ring opening of epoxides: synthesis of 2-hydroxyethers (a typical example). The respective oxide **1** (0.3 mmol) and alcohol **8** (0.6 mmol) were added to a prestirred (10 min) solution of $Sc(OTf)_3$ (3 mg, 6 μmol) and ligand (*S*,*S*)-**L6** (2.5 mg, 6 μmol) in dry CH_2Cl_2 (1.5 ml) in a 4 ml vial. Then the reaction mixture was stirred at 25 °C for the appropriate period of time, usually until **1** was fully consumed (disappearance of the corresponding spot on TLC). Finally, the volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel furnished the desired product.

Racemic mixtures of products were prepared by the same procedure using racemic mixture of Bolm's ligand **L3** and isolated only by preparative TLC.

(*1S,2S*)-2-((4-Methoxybenzyl)oxy)-1,2-diphenylethan-1-ol (9ib)



According to the general procedure with *p*-methoxybenzyl alcohol **8b** (75 µl, 0.6 mmol) for 68 h. Column chromatography of the residue on silica gel (5/1 hexanes/Et_2O) furnished 82 mg (82%, 98% ee) of the title compound as colorless crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26–7.20 (m, 5H, Ar-H), 7.19–7.13 (m, 3H, Ar-H), 7.10–6.99 (m, 4H, Ar-H), 6.92–6.86 (m, 2H, Ar-H), 4,70 (d, *J* = 8.3 Hz, 1H, CH), 4.47 (d, *J* = 11.0 Hz, 1H, CH_2), 4.33 (d, *J* = 8.3 Hz, 1H, CH), 4.27 (d, *J* = 11.0 Hz, 1H, CH_2), 3.83 (s, 3H, CH_3), 3.53 (br s, 1H, OH).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.51, 139.31, 137.81, 129.93, 129.78, 128.28, 128.20, 128.02, 127.94, 127.79, 127.41, 114.04, 86.77, 78.72, 70.63, 55.44.

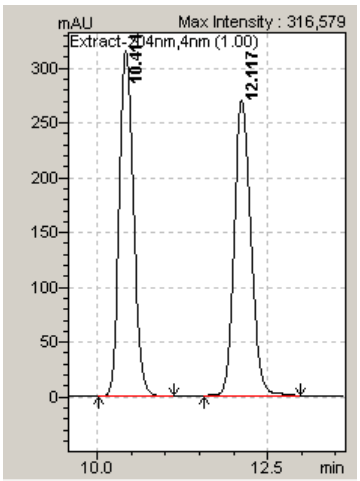
The recorded values were in agreement with the published data.[27]

Daicel Chiralpak IB, *n*-heptane/IPA 95/5, 1 mL/min, 204 nm,

rac-**9ib**: t_1 = 10.4 min, t_2 = 12.1 min;

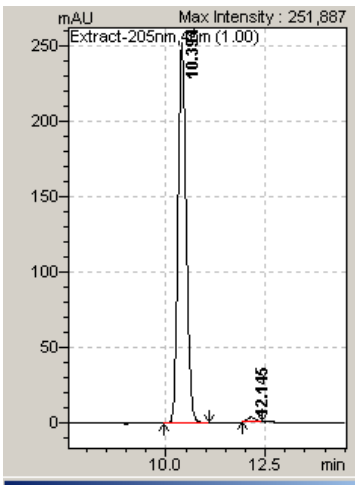
9ib: $t_{S,S}$ = 10.4 min $t_{R,R}$ = 12.1 min.

Figure 15: HPLC of *rac*-**9ib** and (*S,S*)-**9ib**.



Peak Table

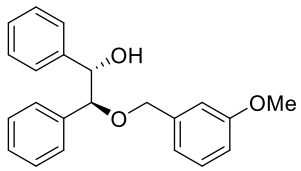
Peak#	ID#	Ret. Time	Area%
1		10.414	49.7632
2		12.117	50.2368



Peak Table

Peak#	ID#	Ret. Time	Area%
1		10.394	98.8236
2		12.145	1.1764

(*1S,2S*)-2-((3-Methoxybenzyl)oxy)-1,2-diphenylethan-1-ol (9if)



According to the general procedure with 3-methoxybenzyl alcohol **8f** (75 µl, 0.6 mmol) for 156 h. Column chromatography of the residue on silica gel (5/1 hexanes/Et_2O) furnished 86 mg (86%, 98% ee) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.13 (m, 7H, Ar-H), 7.21–7.14 (m, 4H, Ar-H), 6.92–6.83 (m, 3H, Ar-H), 4.74 (d, J = 8.2 Hz, 1H, CH), 4.51 (d, J = 11.6 Hz, 1H, CH_2), 4.37 (d, J = 8.2 Hz, 1H, CH), 4.32 (d, J = 11.6 Hz, 1H, CH_2), 3.82 (s, 3H, CH_3), 3.52 (br s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.88, 139.46, 139.29, 137.66, 129.67, 128.31, 128.27, 128.02, 127.97, 127.83, 127.41, 120.28, 113.54, 113.47, 87.06, 78.73, 70.84, 55.38.

IR ν_{max} 3542, 3506, 3434, 3414, 3064, 3028, 2938, 2872, 2833, 1601, 1494, 1458, 1437, 1269, 1198, 1159, 1078, 1057, 1021, 961, 923, 851, 788, 767, 746, 695, 573 cm^{-1}.

HRMS (ESI) *m/z* calculated for $C_{22}H_{23}O_3$ (M+H) 335.1647; found 335.1646.

$[\alpha]_D^{20}$= +16.1° ($CHCl_3$, 0.44 g/100 ml).

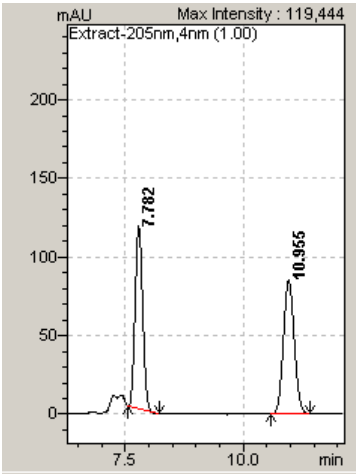
R_f (5/1 hexanes/Et_2O) = 0.25.

Daicel Chiralpak IB, *n*-heptane/IPA 80/20, 1 mL/min, 205 nm,

rac-**9if**: t_1 = 7.8 min, t_2 = 11.0 min;

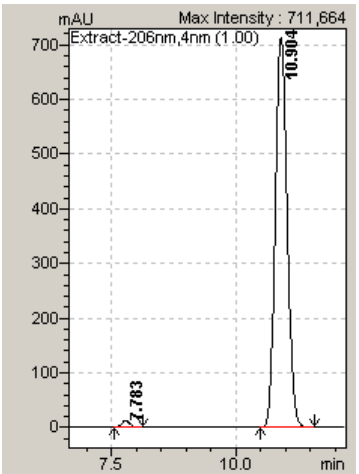
9if: $t_{R,R}$ = 7.8 min $t_{S,S}$ = 10.9 min.

Figure 16: HPLC of *rac*-**9if** and (*S,S*)-**9if**.



Peak Table

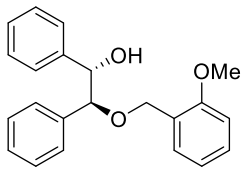
Peak#	ID#	Ret. Time	Area%
1		7.782	48.7218
2		10.955	51.2782



Peak Table

Peak#	ID#	Ret. Time	Area%
1		7.783	1.1980
2		10.904	98.8020

(*1S,2S*)- 2-((2-Methoxybenzyl)oxy)-1,2-diphenylethan-1-ol (9ig)



According to the general procedure with 2-methoxybenzyl alcohol **8g** (80 µl, 0.6 mmol) for 116 h. Column chromatography of the residue on silica gel (5/1 hexanes/Et_2O) furnished 76 mg (76%, 88% ee) of the title compound as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.12 (m, 8H, Ar-H), 7.09–7.00 (m, 4H, Ar-H), 6.99–6.90 (m, 2H, Ar-H), 4.68 (d, *J* = 8.5 Hz, 1H, CH), 4.54 (d, *J* = 11.3 Hz, 1H, CH_2), 4.47 (d, *J* = 11.2 Hz, 1H, CH_2), 4.34 (d, *J* = 8.5 Hz, 1H, CH), 4.00 (br s, 1H, OH), 3.87 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 127.87, 139.35, 137.89, 129.96, 129.57, 128.11, 128.06, 127.97 (2C), 127.91, 127.75, 127.53, 126.08, 120.58, 110.58, 87.58, 78.88, 67.63, 55.43.

Mp = 88-89 °C.

IR (drift KBr) ν_{max} 3405, 3064, 3028, 3001, 2965, 2941, 2899, 2872, 2839, 1607, 1586, 1497, 1455, 1395, 1287, 1245, 1201, 1177, 1126, 1093, 1060, 1033, 934 851 776, 755, 701, 656, 626, 558 cm^{-1}.

HRMS (ESI) *m/z* calculated for $C_{22}H_{22}O_3Na$ (M+Na) 357.14612; found 357.14555.

$[\alpha]_D^{20}$= +25.6° ($CHCl_3$, 0.39 g/100 ml).

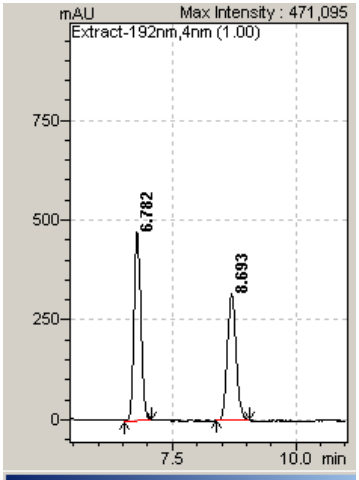
R_f (5/1 hexanes/Et_2O) = 0.30.

Daicel Chiralpak IB, *n*-heptane/IPA 80/20, 1 mL/min, 192 nm,

rac-**9ig**: t_1 = 6.8 min, t_2 = 8.7 min;

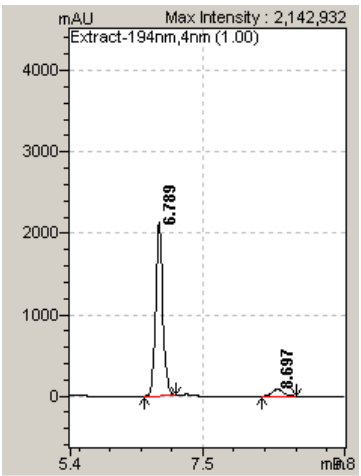
9ig: $t_{S,S}$ = 6.8 min $t_{R,R}$ = 8.7 min.

Figure 17: HPLC of *rac*-**9ig** and (*S,S*)-**9ig**.



Peak Table

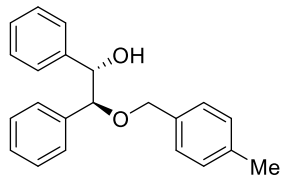
Peak#	ID#	Ret. Time	Area%
1		6.782	53.4879
2		8.693	46.5121



Peak Table

Peak#	ID#	Ret. Time	Area%
1		6.789	94.1660
2		8.697	5.8340

(*1S,2S*)-2-((4-Methylbenzyl)oxy)-1,2-diphenylethan-1-ol (9ih)



According to the general procedure with 4-methylbenzyl alcohol **8h** (74 mg, 0.6 mmol) for 72 h. Column chromatography of the residue on silica gel (5/1 hexanes/Et_2O) furnished 84 mg (88%, 98% ee) of the title compound as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.12 (m, 10H, Ar-H), 7.10–6.99 (m, 4H, Ar-H), 4.77 (d, *J* = 8.0 Hz, 1H, CH), 4.49 (d, *J* = 11.2 Hz, 1H, CH_2), 4.35 (d, *J* = 8.2 Hz, 1H, CH), 4.30 (d, *J* = 11.2 Hz, 1H, CH_2), 3.54 (br s, 1H, OH), 2.37 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.30, 137.80, 137.77, 134.80, 129.33, 128.28, 128.25, 128.21, 128.02, 127.95, 127.80, 127.43, 86.96, 78.76, 70.85, 21.36.

Mp = 71-72 °C.

IR (drift KBr) ν_{max} 3560, 3088, 3031, 2953, 2914, 1866, 1622, 1458, 1395, 1344, 1320, 1260, 1201, 1180, 1081, 1060, 1033, 1021, 1003, 946, 917, 857, 812, 764, 698, 656, 612, 597, 492 cm^{-1}.

HRMS (ESI) *m/z* calculated for $C_{22}H_{23}O_3Na$ (M+Na) 341.15120; found 341.15063.

$[\alpha]_D^{20}$= +23.4° ($CHCl_3$, 0.32 g/100 ml).

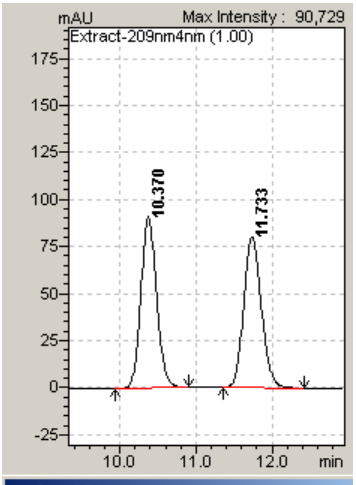
R_f (5/1 hexanes/Et_2O) = 0.53.

Daicel Chiralpak IB, *n*-heptane/IPA 98/2, 1 mL/min, 209 nm,

rac-**9ih**: t_1 = 10.4 min, t_2 = 11.7 min;

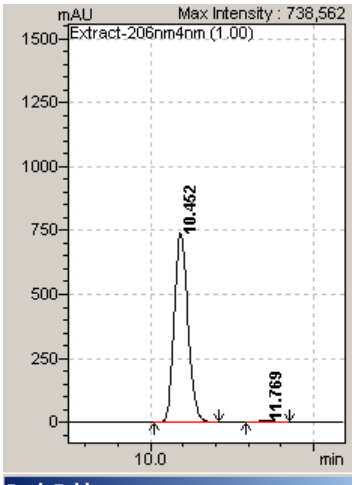
9ih: $t_{S,S}$ = 10.5 min $t_{R,R}$ = 11.8 min.

Figure 18: HPLC of *rac*-**9ih** and (*S,S*)-**9ih**.



Peak Table

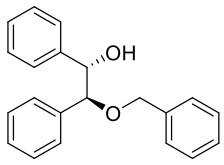
Peak#	ID#	Ret. Time	Area%
1		10.370	49.8418
2		11.733	50.1582



Peak Table

Peak#	ID#	Ret. Time	Area%
1		10.452	98.7782
2		11.769	1.2218

(*1S,2S*)-2-(Benzyloxy)-1,2-diphenylethan-1-ol (9ii)



According to the general procedure with benzyl alcohol **8i** (62 µl, 0.6 mmol) for 91 h. Column chromatography of the residue on silica gel (5/1 hexanes/Et_2O) furnished 80 mg of the title compound (88%, 98% ee) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H, Ar-H), 7.28–7.23 (m, 3H, Ar-H), 7.21–7.15 (m, 3H, Ar-H), 7.12–7.02 (m, 4H, Ar-H), 4.75 (d, *J* = 8.2 Hz, 1H, CH), 4.45 (d, *J* = 11.5 Hz, 1H, CH_2), 4.37 (d, *J* = 7.9 Hz, 1H, CH), 4.35 (d, *J* = 11.2 Hz, 1H, CH_2), 3.55 (br s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.28, 137.85, 137.68, 128.62, 128.29, 128.25, 128.09, 128.00 (2C), 127.96, 127.81, 127.40, 87.08, 78.74, 70.96.

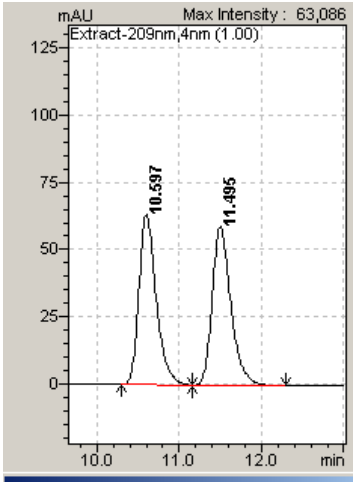
The recorded values were in agreement with the published data.[64]

Daicel Chiralpak IB, *n*-heptane/IPA 98/2, 1 mL/min, 209 nm,

rac-**9ii**: t_1 = 10.6 min, t_2 = 11.5 min;

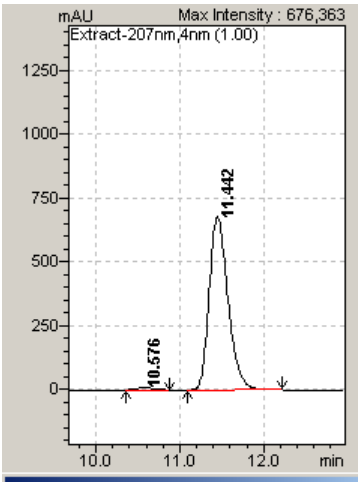
9ii: $t_{R,R}$ = 10.6 min $t_{S,S}$ = 11.4 min.

Figure 19: HPLC of *rac*-**9ii** and (*S,S*)-**9ii**.



Peak Table

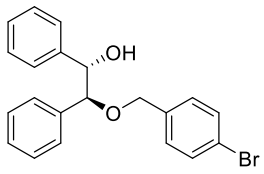
Peak#	ID#	Ret. Time	Area%
1		10.597	49.9601
2		11.495	50.0399



Peak Table

Peak#	ID#	Ret. Time	Area%
1		10.576	1.0951
2		11.442	98.9049

(*1S,2S*)-2-((4-Bromobenzyl)oxy)-1,2-diphenylethan-1-ol (9ij)



According to the general procedure with 4-bromobenzyl alcohol **8j** (112 mg, 0.6 mmol) for 69 h. Column chromatography of the residue on silica gel (5/1 hexanes/Et_2O) furnished 90 mg (78%, 93% ee) of the title compound as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.45 (m, 2H, Ar-H), 7.25–7.20 (m, 3H, Ar-H), 7.19–7.12 (m, 5H, Ar-H), 7.09–7.00 (m, 4H, Ar-H), 4.74 (d, J = 8.0 Hz, 1H, CH), 4.47 (d, J = 11.7 Hz, 1H, CH_2), 4.34 (d, J = 8.0 Hz, 1H), 4.29 (d, J = 11.7 Hz, 1H, CH_2), 3.40 (br s, 1H, OH).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.22, 137.46, 136.85, 131.71, 129.67, 128.37, 128.35, 128.00, 127.94, 127.87, 127.33, 121.87, 87.06, 78.65, 70.14.

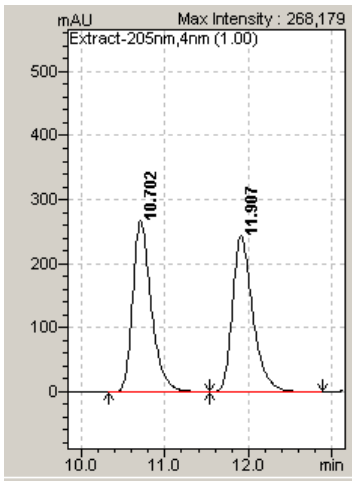
The recorded values were in agreement with the published data.[34]

Daicel Chiralpak IB, *n*-heptane/IPA 98/2, 1 mL/min, 205 nm,

rac-**9ij**: t_1 = 10.7 min, t_2 = 11.9 min;

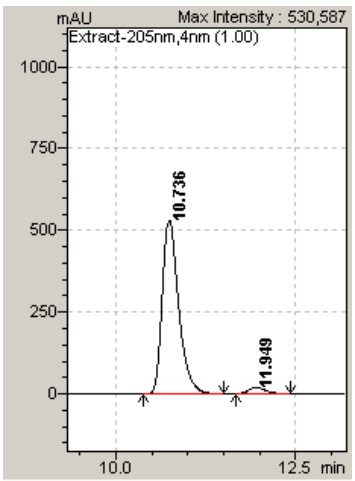
9ij: $t_{S,S}$ = 10.7 min $t_{R,R}$ = 12.0 min.

Figure 20: HPLC of *rac*-**9ij** and (*S,S*)-**9ij**.



Peak Table

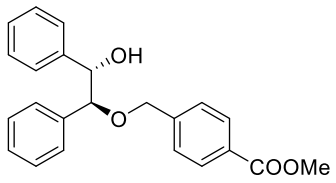
Peak#	ID#	Ret. Time	Area%
1		10.702	50.0560
2		11.907	49.9440



Peak Table

Peak#	ID#	Ret. Time	Area%
1		10.736	96.3659
2		11.949	3.6341

Methyl 4-(((*1S,2S*)-2-hydroxy-1,2-diphenylethoxy)methyl)benzoate (9ik)



According to the general procedure with methyl 4-(hydroxymethyl)benzoate **8k** (100 mg, 0.6 mmol) for 86 h. Column chromatography of the residue on silica gel (2/1 hexanes/Et_2O) furnished 80 mg (76%, 95% ee) of the title compound as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–7.99 (m, 2H, Ar-H), 7.40–7.34 (m, 2H, Ar-H), 7.30–7.14 (m, 6H, Ar-H), 7.12–7.01 (m, 4H, Ar-H), 4.77 (d, *J* = 8.7 Hz, 1H, CH), 4.57 (d, *J* = 12.3 Hz, 1H, CH_2), 4.40 (d, *J* = 12.3 Hz, 1H, CH_2), 4.37 (d, *J* = 8.0 Hz, 1H, CH), 3.93 (s, 3H, CH_3), 3.44 (br s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.01, 143.08, 139.21, 137.38, 129.91, 129.69, 128.40, 128.02, 127.95, 127.90, 127.57, 127.35, 87.31, 78.69, 70.30, 52.28.

Mp = 94-95 °C.

IR (drift KBr) ν_{max} 3494, 3452, 3067, 3028, 2953, 2872, 1721, 1613, 1434, 1284, 1198, 1174, 1105, 1023, 967, 914, 845, 758, 698, 576 cm^{-1}.

HRMS (ESI) *m/z* calculated for $C_{23}H_{22}O_4Na$ (M+Na) 385.14103; found 385.14041.

$[\alpha]_D^{20}$ = +14.1° ($CHCl_3$, 0.39 g/100 ml).

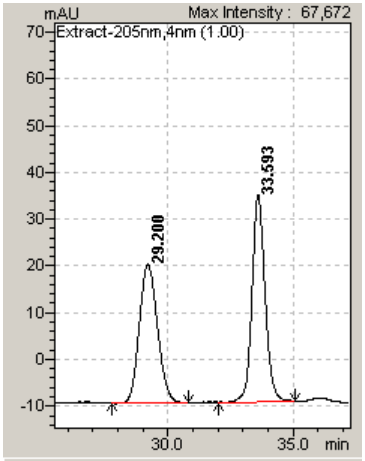
R_f (5/1 hexanes/Et_2O) = 0.10.

Daicel Chiralpak IB, *n*-heptane/IPA 98/2, 1 mL/min, 204 nm,

rac-**9ik**: t_1 = 29.2 min, t_2 = 33.6 min;

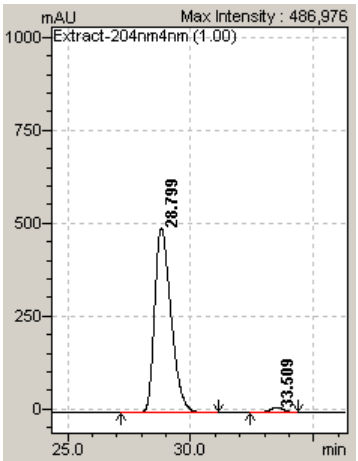
9ik: $t_{S,S}$ = 28.8 min $t_{R,R}$ = 33.5 min.

Figure 21: HPLC of *rac*-**9ik** and (*S,S*)-**9ik**.



Peak Table

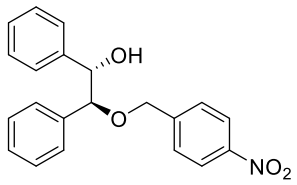
Peak#	ID#	Ret. Time	Area%
1		29.200	48.3608
2		33.593	51.6392



Peak Table

Peak#	ID#	Ret. Time	Area%
1		28.799	97.6703
2		33.509	2.3297

(*1S,2S*)-2-((4-Nitrobenzyl)oxy)-1,2-diphenylethan-1-ol (9il)



According to the general procedure with 4-nitrobenzyl alcohol **8l** (92 mg, 0.6 mmol) for 69 h. Column chromatography of the residue on silica gel (5/1 hexanes/Et_2O) furnished 81 mg (75%, 98% ee) of the title compound as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25–8.16 (m, 2H, Ar-H), 7.50–7.42 (m, 2H, Ar-H), 7.32–7.14 (m, 6H, Ar-H), 7.11–7.01 (m, 4H, Ar-H), 4.81 (d, *J* = 7.8 Hz, 1H, CH), 4.61 (d, *J* = 12.8 Hz, 1H, CH_2), 4.47 (d, *J* = 12.8 Hz, 1H, CH_2), 4.40 (d, *J* = 7.8 Hz, 1H, CH), 3.34 (br s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.59, 145.43, 139.14, 137.13, 128.58, 128.53, 128.10, 128.09, 128.03, 127.89, 127.27, 123.83, 87.58, 78.62, 69.72.

Mp = 76-77 °C.

IR (drift KBr) ν_{max} 3542, 3452, 3114, 3064, 3034, 2872, 1607, 1524, 1494, 4152, 1344, 1317, 1296, 1263, 1251, 1087, 1063, 1042, 1013, 920, 860, 770, 737, 701 cm^{-1}.

HRMS (ESI) *m/z* calculated for $C_{21}H_{20}NO_4$ (M+H) 350.1392; found 350.1389.

$[\alpha]_D^{20}$= + 5.1° (MeOH, 0.39 g/100 ml). (*Note: there is no rotation in $CHCl_3$.)*

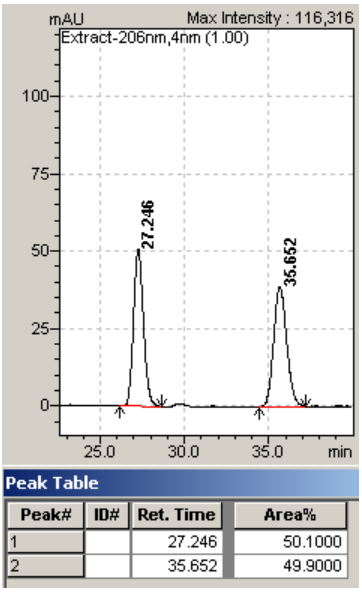
R_f (5/1 hexanes/Et_2O) = 0.21.

Daicel Chiralpak IB, *n*-heptane/IPA 96/4, 1 mL/min, 206 nm,

rac-**9il**: t_1 = 27.2 min, t_2 = 35.7 min;

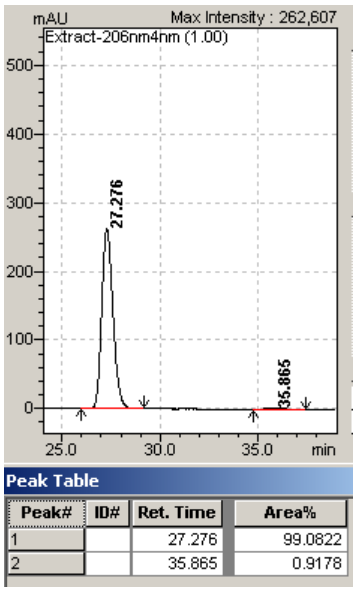
9il: $t_{S,S}$ = 27.3 min $t_{R,R}$ = 35.9 min.

Figure 22: HPLC of *rac*-**9il** and (*S,S*)-**9il**.



Peak Table

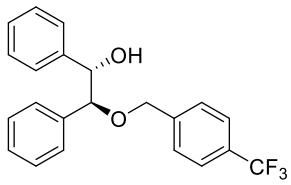
Peak#	ID#	Ret. Time	Area%
1		27.246	50.1000
2		35.652	49.9000



Peak Table

Peak#	ID#	Ret. Time	Area%
1		27.276	99.0822
2		35.865	0.9178

(*1S,2S*)-1,2-Diphenyl-2-((4-(trifluoromethyl)benzyl)oxy)ethan-1-ol (9im)



According to the general procedure with 4-(trifluoromethyl)benzyl alcohol **8m** (83 µl, 0.6 mmol) for 116 h. Column chromatography of the residue on silica gel (5/1 hexanes/Et_2O) furnished 96 mg (86%, 98% ee) of the title compound as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.56 (m, 2H, Ar-H), 7.45–7.37 (m, 2H, Ar-H), 7.30–7.14 (m, 6H, Ar-H), 7.12–7.00 (m, 4H, Ar-H), 4.78 (d, *J* = 8.0 Hz, 1H, CH), 4.57 (d, *J* = 12.3 Hz, 1H, CH_2), 4.41 (d, *J* = 12.3 Hz, 1H, CH_2), 4.39 (d, *J* = 8.0 Hz, 1H, CH), 3.39 (br s, 1H, OH).

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.52.

^{13}C NMR (151 MHz, $CDCl_3$) δ 141.94, 139.19, 137.35, 130.12 (q, $^2J_{C\text{-}F}$ = 32.5 Hz), 128.46, 128.43, 128.05, 127.94 (Cp), 127.33, 125.55 (q, $^3J_{C\text{-}F}$ = 3.5 Hz), 124.26 (q, $^1J_{C\text{-}F}$ = 272.0 Hz), 87.36, 78.68, 70.13.

Mp = 75-76 °C.

IR (drift KBr) ν_{max} 3524, 3402, 3088, 3064, 3034, 2884, 1616, 1458, 1425, 1395, 1326, 1201, 1168, 1123, 1087, 1069, 1021, 911, 857, 821, 776, 755, 701, 665, 576 cm^{-1}.

HRMS (ESI) *m/z* calculated for $C_{22}H_{19}F_3O_2Na$ (M+Na) 395.12294; found 395.12225.

$[\alpha]_D^{20}$ = +7.6° ($CHCl_3$, 0.395 g/100 ml).

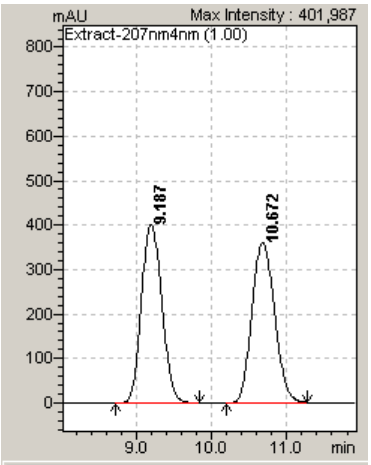
R_f (5/1 hexanes/Et_2O) = 0.35.

Daicel Chiralpak IB, *n*-heptane/IPA 95/5, 1 mL/min, 208 nm,

rac-**9im**: t_1 = 9.2 min, t_2 = 10.7 min;

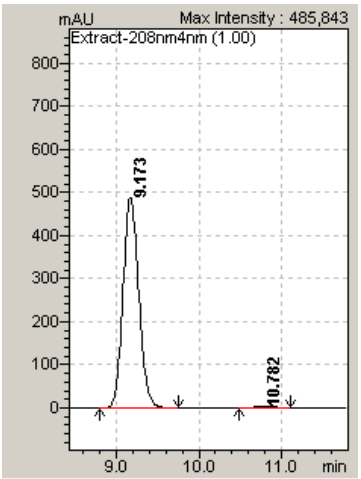
9im: $t_{S,S}$ = 9.2 min $t_{R,R}$ = 10.8 min.

Figure 23: HPLC of *rac*-**9im** and (*S,S*)-**9im**.



Peak Table

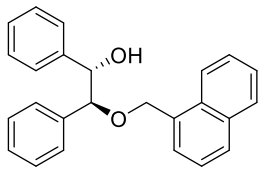
Peak#	ID#	Ret. Time	Area%
1		9.187	49.9888
2		10.672	50.0112



Peak Table

Peak#	ID#	Ret. Time	Area%
1		9.173	98.9562
2		10.782	1.0438

(*1S,2S*)-2-(Naphthalen-1-ylmethoxy)-1,2-diphenylethan-1-ol (9in)



According to the general procedure with naphthalen-1-ylmethanol **8n** (95 mg, 0.6 mmol) for 107 h. Column chromatography of the residue on silica gel (5/1 hexanes/Et_2O) furnished 94 mg (88%, 97% ee) of the title compound as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–8.01 (m, 1H, Ar-H), 7.93–7.82 (m, 2H, Ar-H), 7.59–7.49 (m, 2H, Ar-H), 7.48–7.40 (m, 2H, Ar-H), 7.31–7.24 (m, 3H, Ar-H), 7.20–7.10 (m, 5H, Ar-H), 7.05–6.98 (m, 2H, Ar-H), 4.99 (d, *J* = 11.5 Hz, 1H, CH_2), 4.78 (d, *J* = 11.5 Hz, 1H, CH_2), 4.74 (d, *J* = 8.3 Hz, 1H, CH), 4.45 (d, *J* = 8.2 Hz, 1H, CH), 3.42 (br s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.26, 137.70, 133.95, 133.32, 131.95, 129.09, 128.85, 128.35, 128.34, 128.11, 127.95, 127.80, 127.39, 127.07, 126.62, 126.03, 125.36, 123.87, 87.35, 78.67, 69.42.

Mp = 73-74 °C.

IR (drift KBr) ν_{max} 3554, 3476, 3440, 3064, 3028, 2881, 1598, 1515, 1488, 1452, 1392, 1257, 1231, 1201, 1171, 1090, 1066, 1042, 1021, 917, 857, 800, 767, 701, 564, 555 cm^{-1}.

HRMS (ESI) *m/z* calculated for $C_{25}H_{22}O_2Na$ (M+Na) 377.15120; found 377.15095.

$[\alpha]_D^{20}$= +53.1 ($CHCl_3$, 0.32 g/100 ml).

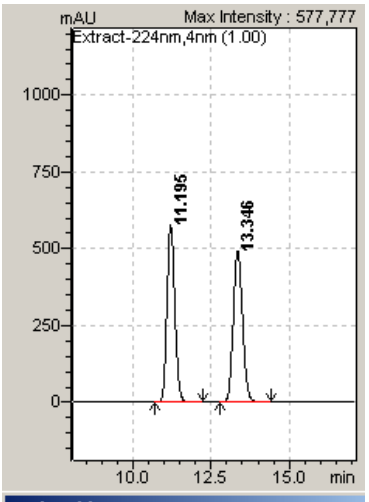
R_f (5/1 hexanes/Et_2O) = 0.33.

Daicel Chiralpak IB, *n*-heptane/IPA 80/20, 1 mL/min, 224 nm,

rac-**9in**: t_1 = 11.2 min, t_2 = 13.4 min;

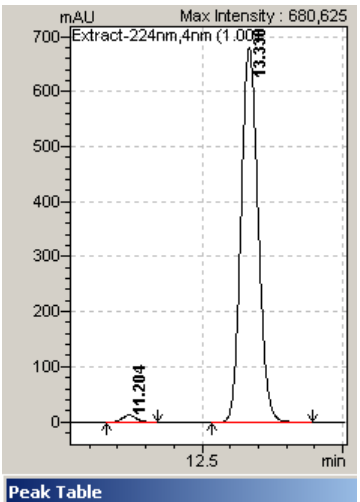
9in: $t_{R,R}$ = 11.2 min, $t_{S,S}$ = 13.3 min.

Figure 24: HPLC of *rac*-**9in** and (*S,S*)-**9in**.



Peak Table

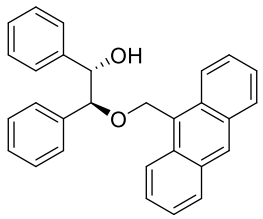
Peak#	ID#	Ret. Time	Area%
1		11.195	49.7525
2		13.346	50.2475



Peak Table

Peak#	ID#	Ret. Time	Area%
1		11.204	1.4632
2		13.330	98.5368

(*1S,2S*)-2-(Anthracen-9-ylmethoxy)-1,2-diphenylethan-1-ol (9io)



According to the general procedure with 9-antharecenemethanol **8o** (125 mg, 0.6 mmol) at 40 °C for 69 h. Column chromatography of the residue on silica gel (5/1 hexanes/Et_2O) furnished 76 mg (63%, 96% ee) of the title compound as yellowish crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H, Ar-H), 8.19–8.13 (m, 2H, Ar-H), 8.07–8.01 (m, 2H, Ar-H), 7.55–7.45 (m, 4H, Ar-H), 7.38–7.30 (m, 3H, Ar-H), 7.23–7.11 (m, 5H, Ar-H), 7.03–6.98 (m, 2H, Ar-H), 5.46 (d, *J* = 11.2 Hz, 1H, CH_2), 5.34 (d, *J* = 11.1 Hz, 1H, CH_2), 4.69 (d, *J* = 8.2 Hz, 1H, CH), 4.52 (d, *J* = 8.2 Hz, 1H, CH), 3.37 (br s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.18, 138.04, 131.59, 131.18, 129.27, 128.87, 128.51, 128.42, 128.26, 128.19, 127.95, 127.78, 127.37, 126.61, 125.19, 124.14, 87.81, 78.66, 63.41.

Mp = 143-144 °C.

IR (drift KBr) ν_{max} 3509, 3458, 3058, 3031, 2887, 2863, 162, 1452, 1335, 1254, 1234, 1201, 1177, 1156, 1081, 1066, 1048, 1018, 1003, 985, 884, 848, 767, 734, 698, 585, 555 cm^{-1}.

HRMS (ESI) *m/z* calculated for $C_{29}H_{24}O_2$ (M+H) 404.1776; found 404.1771.

$[\alpha]_D^{20}$ = + 101.6° ($CHCl_3$, 0.31 g/100 ml).

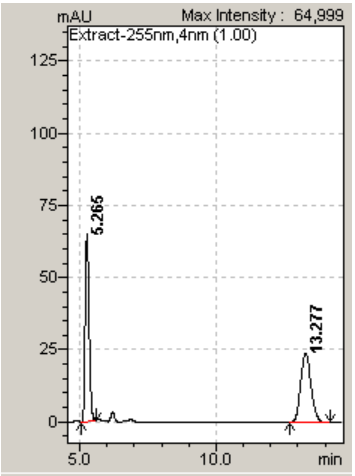
R_f (5/1 hexanes/Et_2O) = 0.20.

Daicel Chiralpak IB, *n*-heptane/IPA 50/50, 1 mL/min, 255 nm,

rac-**9io**: t_1 = 5.3 min, t_2 = 13.2 min;

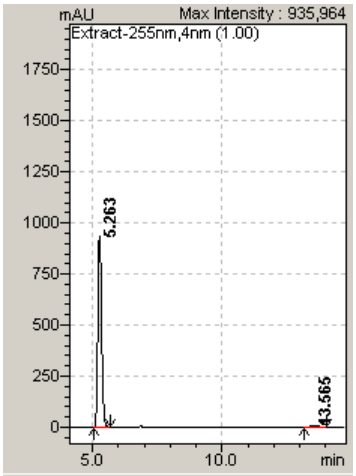
9io: $t_{S,S}$ = 5.3 min, $t_{R,R}$ = 13.6 min.

Figure 25: HPLC of *rac*-**9io** and (*S,S*)-**9io**.



Peak Table

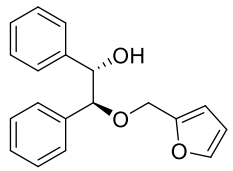
Peak#	ID#	Ret. Time	Area%
1		5.265	49.9449
2		13.277	50.0551



Peak Table

Peak#	ID#	Ret. Time	Area%
1		5.263	98.2326
2		13.565	1.7674

(*1S,2S*)-1,2-Diphenyl-2-(furan-2-ylmethoxy)ethan-1-ol (9ip)



According to the general procedure with furfuryl alcohol **8p** (52 µl, 0.6 mmol) for 23 days. Reaction carried out with powdered 4Å MS (30 mg) and furnished desired alcohol **9ip** (75% ^{1}H NMR yield, 97% ee) as a colorless oil. The product was isolated by preparative TLC for HPLC.

A reaction without 4Å MS. According to the general procedure with furfuryl alcohol **8p** (52 µl, 0.6 mmol) for 69 h. Column chromatography of the residue on silica gel (10/1 hexanes/EtOAc) furnished 52 mg of the title compound (61%, 85% ee) as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 1.8, 0.8 Hz, 1H, Ar-H), 7.25–7.11 (m, 6H, Ar-H), 7.08–6.97 (m, 4H, Ar-H), 6.45 (dd, *J* = 3.3, 0.75 Hz, 1H, Ar-H), 6.26 (d, *J* = 3.3 Hz, 1H, Ar-H), 4.69 (d, *J* = 8.3 Hz, 1H, CH), 4.50 (d, *J* = 12.7 Hz, 1H, CH_2), 4.31 (d, *J* = 8.4 Hz, 1H, CH), 4.28 (d, *J* = 12.7 Hz, 1H, CH_2), 3.52 (s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.33, 143.19, 139.16, 137.34, 128.27 (2C), 128.04 , 127.95, 127.83, 127.46, 110.42, 109.76, 86.71, 78.61, 62.84.

IR (drift KBr) ν_{max} 3569, 3539, 3512, 3461, 3431, 3372, 3064, 3028, 2923, 2893, 2866, 1601, 1497, 1455, 1260, 1228, 1198, 1153, 1069, 1021, 984, 949, 923, 890, 851, 815, 752, 701, 647, 576 cm^{-1}.

HRMS (ESI) *m/z* calculated for $C_{19}H_{19}O_3$ (M+H) 295.1335; found 295.1334.

$[\alpha]_D^{20}$= +45.7° ($CHCl_3$, 0.35 g/100 ml).

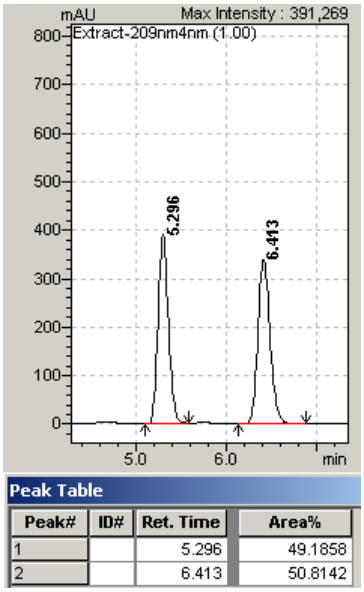
R_f (5/1 hexanes/EtOAc) = 0.20.

Daicel Chiralpak IB, *n*-heptane/IPA 80/20, 1 mL/min, 209 nm,

rac-**9ip**: t_1 = 5.3 min, t_2 = 6.4 min;

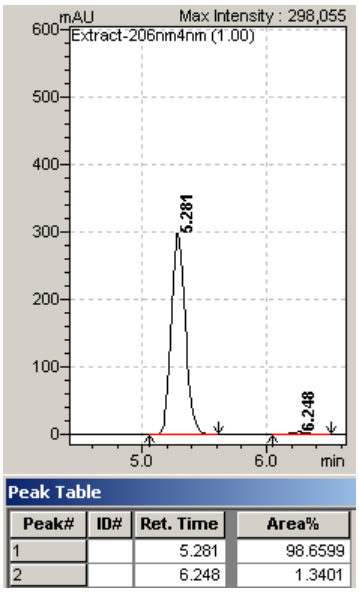
9ip: $t_{S,S}$ = 5.3 min $t_{R,R}$ = 6.4 min.

Figure 26: HPLC of *rac*-**9ip** and (*S,S*)-**9ip**.



Peak Table

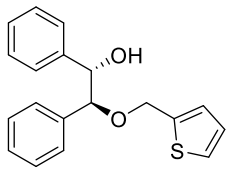
Peak#	ID#	Ret. Time	Area%
1		5.296	49.1858
2		6.413	50.8142



Peak Table

Peak#	ID#	Ret. Time	Area%
1		5.281	98.6599
2		6.248	1.3401

(*1S,2S*)-1,2-Diphenyl-2-(thiophen-2-ylmethoxy)ethan-1-ol (9iq)



According to the general procedure with thiophenyl-2-ylmethanol **8q** (57 µl, 0.6 mmol) for 114 h. Column chromatography of the residue on silica gel (20/1 hexanes/EtOAc) furnished 79 mg (85%, 97% ee) of the title compound as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 5.1, 1.2 Hz, 1H, Ar-H), 7.28–7.21 (m, 3H, Ar-H,), 7.19–7.11 (m, 3H, Ar-H), 7.09–6.98 (m, 5H, Ar-H), 6.95-6.93 (m, 1H, Ar-H), 4.70-4.66 (m, 2H, CH+CH_2), 4.52 (d, *J* = 12.2 Hz, 1H, CH_2), 4.38 (d, *J* = 8.3 Hz, 1H, CH), 3.47 (br s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.49, 139.16, 137.35, 128.34 (2C), 128.06, 127.96, 127.84, 127.44, 126.87, 126.79, 126.27, 86.60, 78.60, 65.27.

Mp = 61-62 °C.

IR (drift KBr) ν_{max} 3530, 3106, 3058, 3031, 2938, 2887, 2860, 1957, 1882, 1817, 1491, 1452, 1932, 1335, 1269, 1222, 1198, 1177, 1069, 1045, 1021, 994, 920, 860, 824, 776, 755, 704, 656, 632, 612, 555, 540, 480, 462 cm^{-1}.

HRMS (ESI) *m/z* calculated for $C_{19}H_{19}O_2S$ 311.1106 (M+H); found 311.1113.

$[\alpha]_D^{20}$= +46.7° ($CHCl_3$, 0.54 g/100 ml).

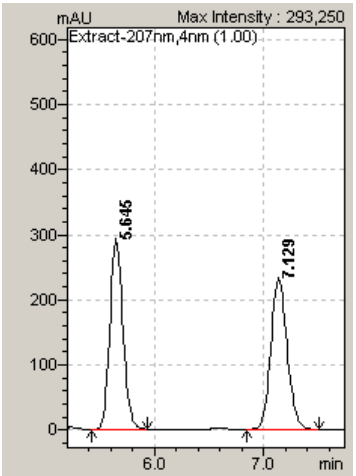
R_f (10/1 hexanes/EtOAc) = 0.20.

Daicel Chiralpak IB, *n*-heptane/IPA 80/20, 1 mL/min, 207 nm,

rac-**9iq**: t_1 = 5.6 min, t_2 = 7.1 min;

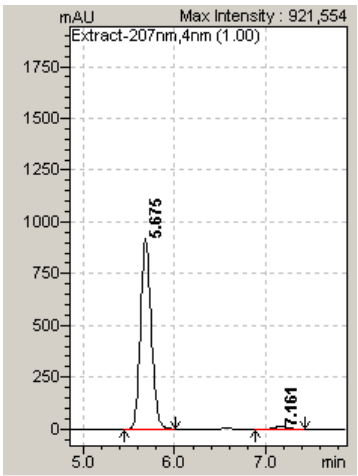
9iq: $t_{S,S}$ = 5.7 min $t_{R,R}$ = 7.1 min.

Figure 27: HPLC of *rac*-**9iq** and (*S,S*)-**9iq**.



Peak Table

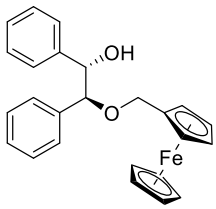
Peak#	ID#	Ret. Time	Area%
1		5.645	49.9751
2		7.129	50.0249



Peak Table

Peak#	ID#	Ret. Time	Area%
1		5.675	98.5096
2		7.161	1.4904

(1*S*,2*S*)-1,2-Diphenyl-2-(ferrocenylmethoxy)ethan-1-ol (9ir)



According to the general procedure with ferrocenyl methanol **8r** (135 mg, 0.6 mmol) for 11 days. Column chromatography of the residue on silica gel (5/1 hexanes/Et_2O) furnished 35 mg (27%, 89% ee) of the title compound as orange crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.12 (m, 6H, Ar-H), 7.07–6.95 (m, 4H, Ar-H), 4.62 (d, *J* = 8.3 Hz, 1H, CH), 4.30 (d, *J* = 8.2 Hz, 1H, CH), 4.29 (d, *J* = 11.2 Hz, 1H, $FcCH_2$), 4.25–4.17 (m, 4H, Cp) 4.14 (d, *J* = 11.2 Hz, 1H, $FcCH_2$), 4.10 (s, 5H, Cp), 3.53 (br s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.28, 137.91, 128.22, 128.14, 127.98, 127.93, 127.78, 127.45, 86.79, 83.32, 78.71, 69.53, 69.19, 68.94, 68.66, 67.38.

Mp = 108-109 °C.

IR (drift KBr) ν_{max} 3560, 3545, 3464, 3446, 3091, 3064, 3028, 2926, 2866, 1658, 1604, 1449, 1413, 1237, 1201, 1108, 1072, 1021, 1003, 923, 824, 770, 698, 576, 504 cm^{-1}.

HRMS (ESI) *m*/*z* calculated for $C_{25}H_{25}FeO_2$ (M+Na) 435.10179; found 435.10152.

$[\alpha]_D^{20}$= 52.1° ($CHCl_3$, 0.48 g/100 ml).

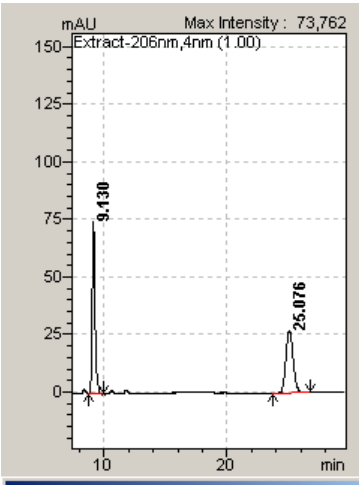
R_f (5/1 hexanes/EtOAc) = 0.20.

Daicel Chiralpak IB, *n*-heptane/IPA 90/10, 1 mL/min, 206 nm,

rac-**9ir**: t_1 = 9.1 min, t_2 = 25.1 min;

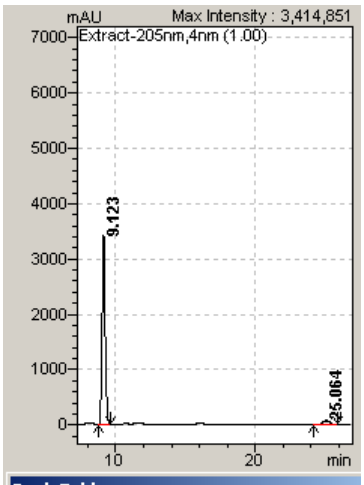
9ir: $t_{S,S}$ = 9.1 min $t_{R,R}$ = 25.1 min.

Figure 28: HPLC of *rac*-**9ir** and (*S,S*)-**9ir**.



Peak Table

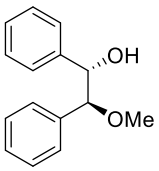
Peak#	ID#	Ret. Time	Area%
1		9.130	51.7080
2		25.076	48.2920



Peak Table

Peak#	ID#	Ret. Time	Area%
1		9.123	94.5137
2		25.064	5.4863

(1*S*,2*S*)-2-Methoxy-1,2-diphenylethan-1-ol (9ic)



According to the general procedure with methanol **8c** (25 µl, 0.6 mmol) for 86 h. Column chromatography of the residue on silica gel (5/1 hexanes/Et_2O) furnished 59 mg (87%, 93% ee) of the title compound as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.12 (m, 6H, Ar-H), 7.07–6.96 (m, 4H, Ar-H), 4.66 (d, J = 8.3 Hz, 1H, CH), 4.13 (d, J = 8.3 Hz, 1H, CH), 3.52 (br s, 1H, OH), 3.31 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.32, 137.54, 128.19, 128.15, 127.97, 127.90, 127.83, 127.43, 89.35, 78.81, 57.05.

R_f (5/1 hexanes/Et_2O) = 0.20.

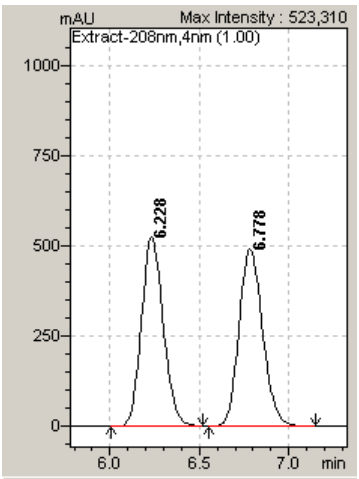
The recorded values were in agreement with the published data.[27]

Daicel Chiralpak IB, *n*-heptane/IPA 90/10, 1 mL/min, 208 nm,

rac-**9ic**: t_1 = 6.2 min, t_2 = 6.8 min;

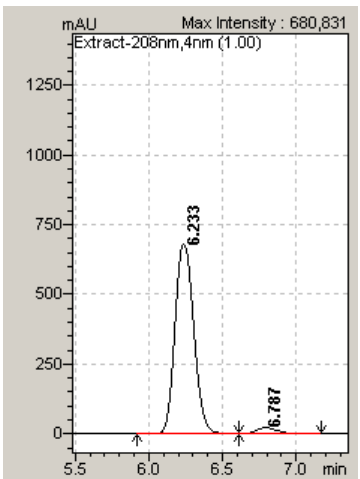
9ic: $t_{S,S}$ = 6.2 min $t_{R,R}$ = 6.8 min.

Figure 29: HPLC of *rac*-**9ic** and (*S,S*)-**9ic**.



Peak Table

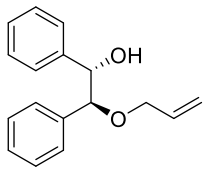
Peak#	ID#	Ret. Time	Area%
1		6.228	49.7504
2		6.778	50.2496



Peak Table

Peak#	ID#	Ret. Time	Area%
1		6.233	96.4546
2		6.787	3.5454

(1*S*,2*S*)-2-(Allyloxy)-1,2-diphenylethan-1-ol (9id)



According to the general procedure with allyl alcohol **8d** (41 µl, 0.6 mmol) for 86 h. Column chromatography of the residue on silica gel (5/1 hexanes/Et_2O) furnished 65 mg (86%, 95% ee) of the title compound as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.12 (m, 6H, Ar-H), 7.07–6.96 (m, 4H, Ar-H), 5.99–5.84 (m, 1H, CH), 5.32–5.10 (m, 2H, $=CH_2$), 4.69 (d, J = 8.4 Hz, 1H, CH), 4.30 (d, J = 8.3 Hz, 1H, CH), 4.00 (app ddt, J = 12.6, 5.1, 1.3 Hz, 1H, CH_2), 3.85 (app ddt, J = 12.6, 6.1, 1.3 Hz 1H, CH_2), 3.54 (br s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.29, 137.72, 134.45, 128.20, 128.16, 127.97, 127.92, 127.84, 127.45, 117.46, 86.91, 78.74, 69.90.

R_f (5/1 hexanes/Et_2O) = 0.30.

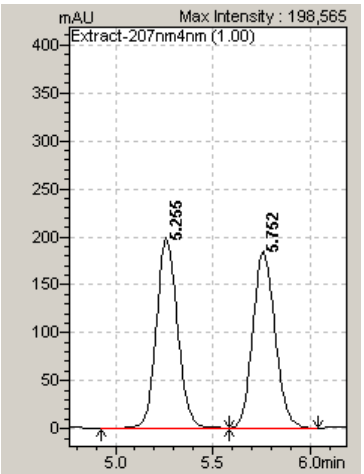
The recorded values were in agreement with the published data.[27]

Daicel Chiralpak IB, *n*-heptane/IPA 90/10, 1 mL/min, 207 nm,

rac-**9id**: t_1 = 5.3 min, t_2 = 5.8 min;

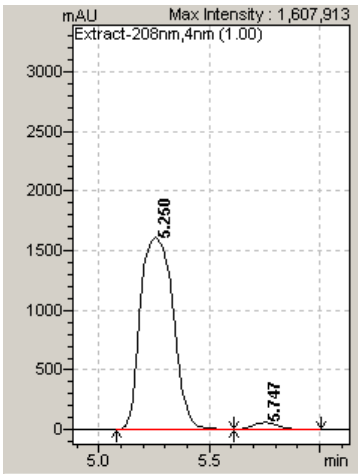
9id: $t_{S,S}$ = 5.3 min $t_{R,R}$ = 5.8 min.

Figure 30: HPLC of *rac*-**9id** and (*S,S*)-**9id**.



Peak Table

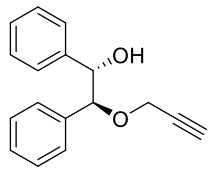
Peak#	ID#	Ret. Time	Area%
1		5.255	50.5735
2		5.752	49.4265



Peak Table

Peak#	ID#	Ret. Time	Area%
1		5.250	97.3321
2		5.747	2.6679

(*1S,2S*)-1,2-Diphenyl-2-(prop-2-yn-1-yloxy)ethan-1-ol (9ie)



According to the general procedure with propargyl alcohol **8e** (35 µl, 0.6 mmol) for 96 h. Column chromatography of the residue on silica gel (5/1 hexanes/Et_2O) furnished 65 mg (81%, 98% ee) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.12 (m, 6H, Ar-H), 7.10–6.98 (m, 4H, Ar-H), 4.73 (d, J = 8.4 Hz, 1H, CH), 4.51 (d, J = 8.4 Hz, 1H, CH), 4.22 (dd, J = 15.7, 2.3 Hz 1H, CH_2), 3.95 (dd, J = 15.7, 2.2 Hz 1H, CH_2), 3.45 (s, 1H, OH), 2.46 (t, J = 2.2 Hz, 1H, ≡CH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.08, 136.61, 128.46, 128.32, 128.11, 127.99, 127.91, 127.47, 86.30, 79.41, 78.39, 75.04, 56.14.

R_f (5/1 hexanes/Et_2O) = 0.20.

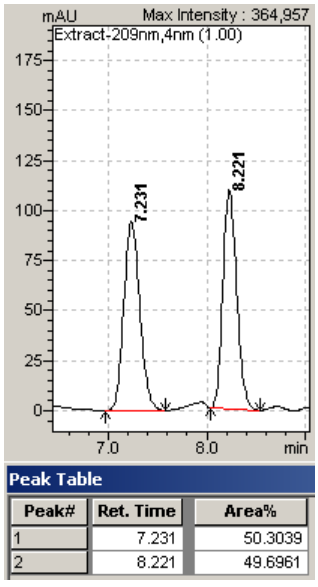
The recorded values were in agreement with the published data.[27]

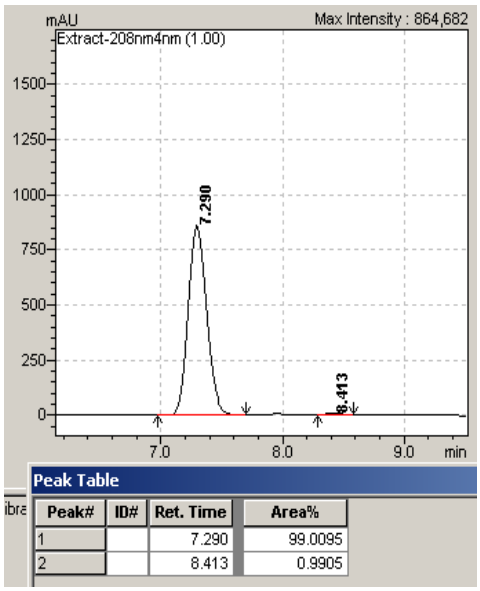
Daicel Chiralpak IB, *n*-heptane/IPA 90/10, 1 mL/min, 208 nm,

rac-**9ie**: t_1 = 7.2 min, t_2 = 8.2 min;

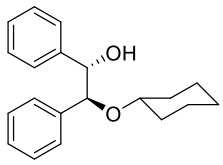
9ie: $t_{S,S}$ = 7.3 min, $t_{R,R}$ = 8.4 min.

Figure 31: HPLC of *rac*-**9ie** and (*S,S*)-**9ie**.





(1*S*,2*S*)-2-(Cyclohexyloxyl)-1,2-diphenylethan-1-ol (9is)



According to the general procedure with cyclohexanol **8s** (60 µl, 0.6 mmol) for 23 days in the presence of powdered MS 4Å. Column chromatography of the residue on silica gel (20/1 hexanes/Et_2O) furnished 74 mg (83%, 99% ee) of the title compound as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.13 (m, 6H, Ar-H), 7.07–6.98 (m, 4H, Ar-H), 4.59 (d, *J* = 8.1 Hz, 1H, CH), 4.35 (d, *J* = 8.1 Hz, 1H, CH), 3.60 (br s, 1H, OH), 3.32–3.23 (m, 1H, CH), 1.80–1.60 (m, 3H, CH_2), 1.52–1.08 (m, 7H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.57, 139.05, 128.01, 127.91, 127.86, 127.85, 127.74, 127.44, 84.70, 78.80, 75.72, 33.67, 31.50, 25.83, 24.21, 24.03.

Mp = 55-56 °C.

IR (drift KBr) ν_{max} 3524, 3061, 3031, 3029, 2887, 2860, 1491, 1449, 1389, 1320, 1260, 1225, 1195, 1084, 1069, 1024, 961, 911, 890, 851, 776, 749, 701, 662, 573 cm^{-1}.

HRMS (ESI) *m*/*z* calculated for $C_{20}H_{25}O_2$ (M+H) 297.1855; found 297.1856.

$[\alpha]_D^{20}$ = 11.5° ($CHCl_3$, 0.31 g/100 ml).

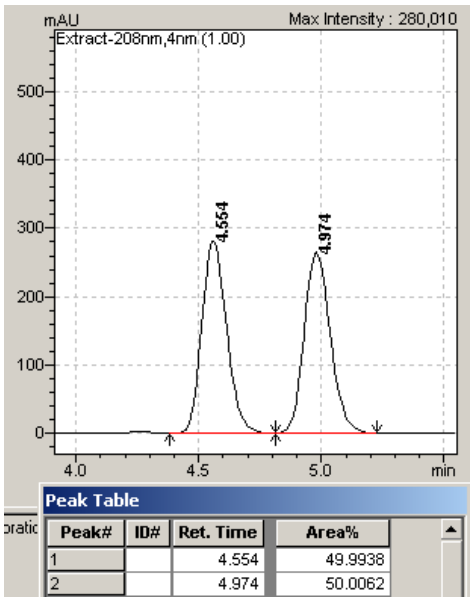
R_f (5/1 hexanes/EtOAc) = 0.30.

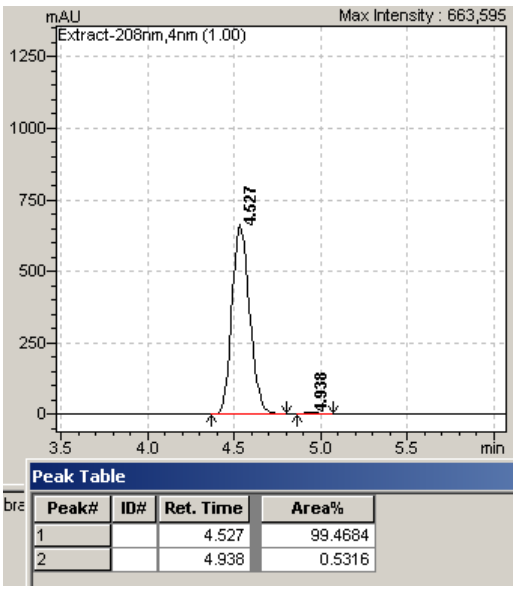
Daicel Chiralpak IB, *n*-heptane/IPA 90/10, 1 mL/min, 208 nm,

rac-**9is**: t_1 = 4.6 min, t_2 = 5.0 min;

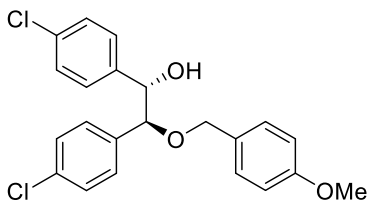
9is: $t_{S,S}$ = 4.5 min $t_{R,R}$ = 5.0 min.

Figure 32: HPLC of *rac*-**9is** and (*S,S*)-**9is**.





(1*S*,2*S*)-1,2-Bis(4-chlorophenyl)-2-((4-methoxybenzyl)oxy)ethan-1-ol (9pb)



According to the general procedure with *p*-methoxybenzyl alcohol **8b** (75 µL, 0.6 mmol) for 6 days. Column chromatography of the residue on silica gel (gradient hexanes/EtOAc 30/1 to 15/1) furnished 80 mg (67%, 97% ee) of the title compound as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.13 (m, 6H, Ar-H), 7.01–6.87 (m, 6H, Ar-H), 4.63 (d, J = 8.2 Hz, 1H, CH), 4.44 (d, J = 11.0 Hz, 1H, CH_2), 4.27-4.25 (m, 2H, CH+CH_2), 3.83 (s, 3H, CH_3), 3.48 (br s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.65, 137.54, 136.08, 134.18, 133.70, 129.84, 129.41, 129.31, 128.72, 128.69, 128.26, 114.11, 85.84, 77.97, 70.79, 55.45.

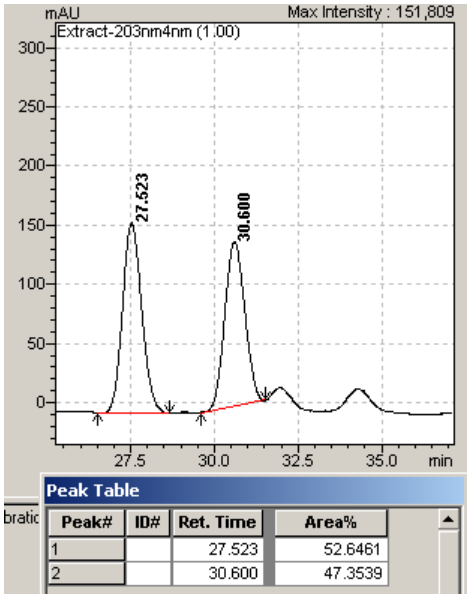
The recorded values were in agreement with the published data.[27]

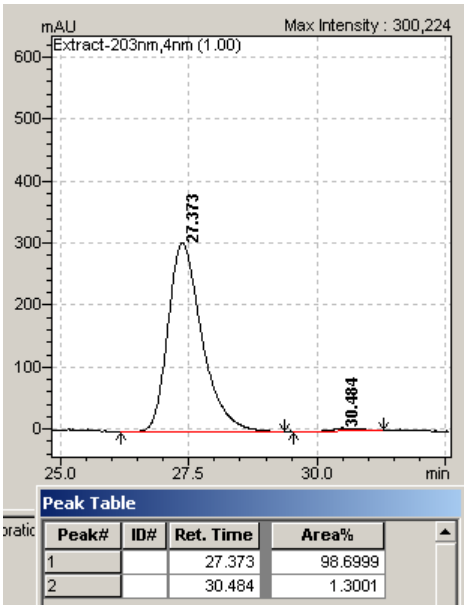
Daicel Chiralpak IB, *n*-heptane/IPA 99/1, 1 mL/min, 203 nm,

rac-**9ie**: t_1 = 27.5 min, t_2 = 30.6 min;

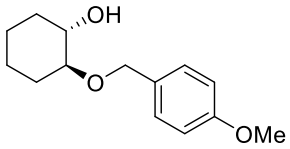
9ie: $t_{S,S}$ = 27.4 min, $t_{R,R}$ = 30.5 min.

Figure 33: HPLC of *rac*-**9ie** and (*S,S*)-**9ie**.





(1*S*,2*S*)-2-((4-Methoxybenzyl)oxy)cyclohexan-1-ol (9ab)



According to the general procedure with *p*-methoxybenzyl alcohol **8b** (75 µL, 0.6 mmol) for 3 days at -20 °C. The reaction furnished the title compound (70% ^{1}H NMR yield, 31% ee). The product was isolated by preparative TLC for HPLC.

A reaction with 10 mol% of the catalytic system. According to this procedure with 10 mol% load of catalyst at 30 °C. Column chromatography of the residue on silica gel (10/1 hexanes/EtOAc) furnished 20 mg of the title compound (30 %, 42% ee) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.23 (m, 2H, Ar-H), 6.92–6.86 (m, 2H, Ar-H), 4.63 (d, J = 11.1 Hz, 1H, CH_2), 4.40 (d, J = 11.1 Hz, 1H, CH_2), 3.80 (s, 3H, CH_3), 3.51–3.41 (m, 1H, CH), 3.21–3.11 (m, 1H, CH), 2.64 (brs, 1H, OH), 2.16–2.09 (m, 1H, CH_2), 2.04–1.97 (m, 1H, CH_2), 1.77–1.66 (m, 2H, CH_2), 1.34–1.14 (m, 4H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.41, 130.83, 129.52, 114.07, 83.38, 73.94, 70.63, 55.44, 32.15, 29.35, 24.43, 24.11.

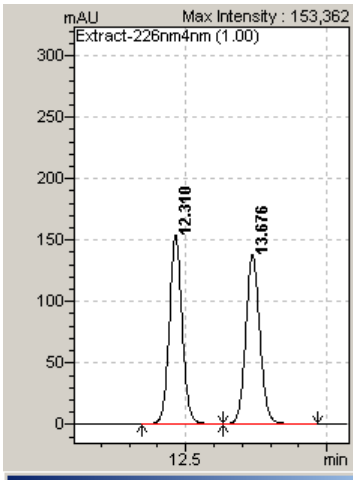
The recorded values were in agreement with the published data.[27]

Daicel Chiralpak IA, *n*-heptane/IPA 95/5, 1 mL/min, 226 nm,

rac-**9ab**: t_1 = 12.3 min, t_2 = 13.7 min;

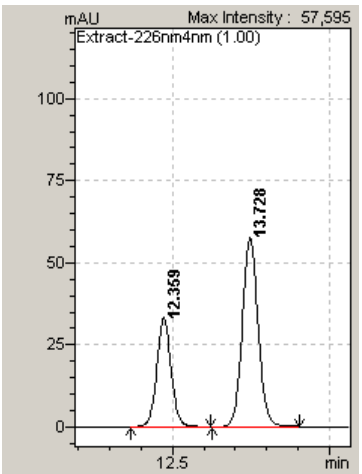
9ab: $t_{R,R}$ = 12.3 min $t_{S,S}$ = 13.7 min.

Figure 34: HPLC of *rac*-**9ab** and (*S,S*)-**9ab**.



Peak Table

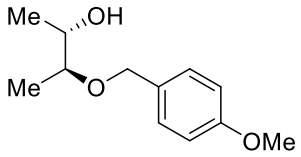
Peak#	ID#	Ret. Time	Area%
1		12.310	50.1110
2		13.676	49.8890



Peak Table

Peak#	ID#	Ret. Time	Area%
1		12.359	34.4757
2		13.728	65.5243

(2*S*,3*S*)-3-((4-Methoxybenzyl)oxy)butan-2-ol (9db)



According to the general procedure with *p*-methoxybenzyl alcohol **8b** (75 µL, 0.6 mmol) for 3 days at -20 °C. The reaction furnished the title compound (40% ^{1}H NMR yield, 52% ee). The product was isolated by preparative TLC for HPLC.

A reaction with 10 mol% of the catalytic system. According to this procedure with 10 mol% load of catalyst at 30 °C. Column chromatography of the residue on silica gel (10/1 hexanes/EtOAc) furnished 54 mg of the title compound (75 %, 42% ee) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.23 (m, 2H, Ar-H), 6.91–6.86 (m, 2H, Ar-H), 4.61 (d, J = 11.1 Hz, 1H, CH_2), 4.37 (d, J = 11.1 Hz, 1H, CH_2), 3.81 (s, 3H, CH_3), 3.64–3.55 (m, 1H, CH), 3.33–3.24 (m, 1H, CH), 2.71 (br s, 1H, OH), 1.18-1.15 (m, 6H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.44, 130.54, 129.56, 114.05, 80.06, 71.33, 70.86, 55.43, 18.66, 15.56.

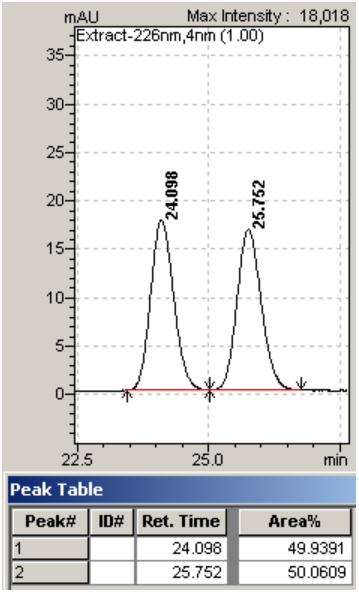
The recorded values were in agreement with the published data.[27]

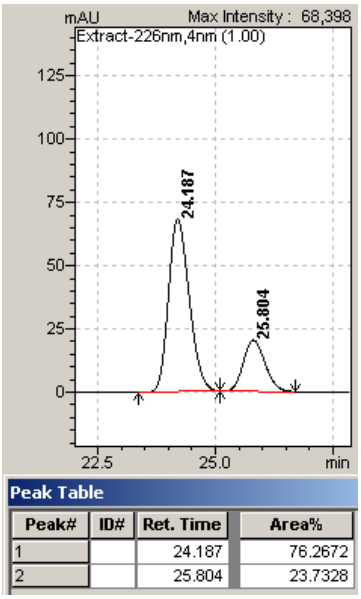
Daicel Chiralpak IB, *n*-heptane/IPA 99.1/0.1, 1 mL/min, 35 °C, 226 nm,

rac-**9db**: t_1 = 24.1 min, t_2 = 25.8 min;

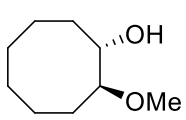
9db: $t_{S,S}$ = 24.2 min, $t_{R,R}$ = 25.8 min.

Figure 35: HPLC of *rac*-**9db** and (*S,S*)-**9db**.





(1*S*,2*S*)-2-Methoxycyclooctan-1-ol (9wc)



cis-Cyclooctene oxide **8c** (40 mg, 0.3 mmol) was added to the prestirred (10 min) solution of $Sc(OTf)_3$ (15 mg; 0.03 mmol) and (*S*,*S*)-**L6** (13 mg; 0.03 mmol) in dry MeOH (1.5 ml) in a 4 ml vial . After stirring at 70 °C for 20 h, the oxide **1w** was fully consumed (disappearance of the respective spot on TLC) and the volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (10/1 DCM/EtOAc) furnished 39 mg of the title compound (85%) as a colorless oil. ^{19}F NMR of the corresponding Mosher esters showed 96% ee (δ -71.47 (2 %), -71.67 (98 %)).

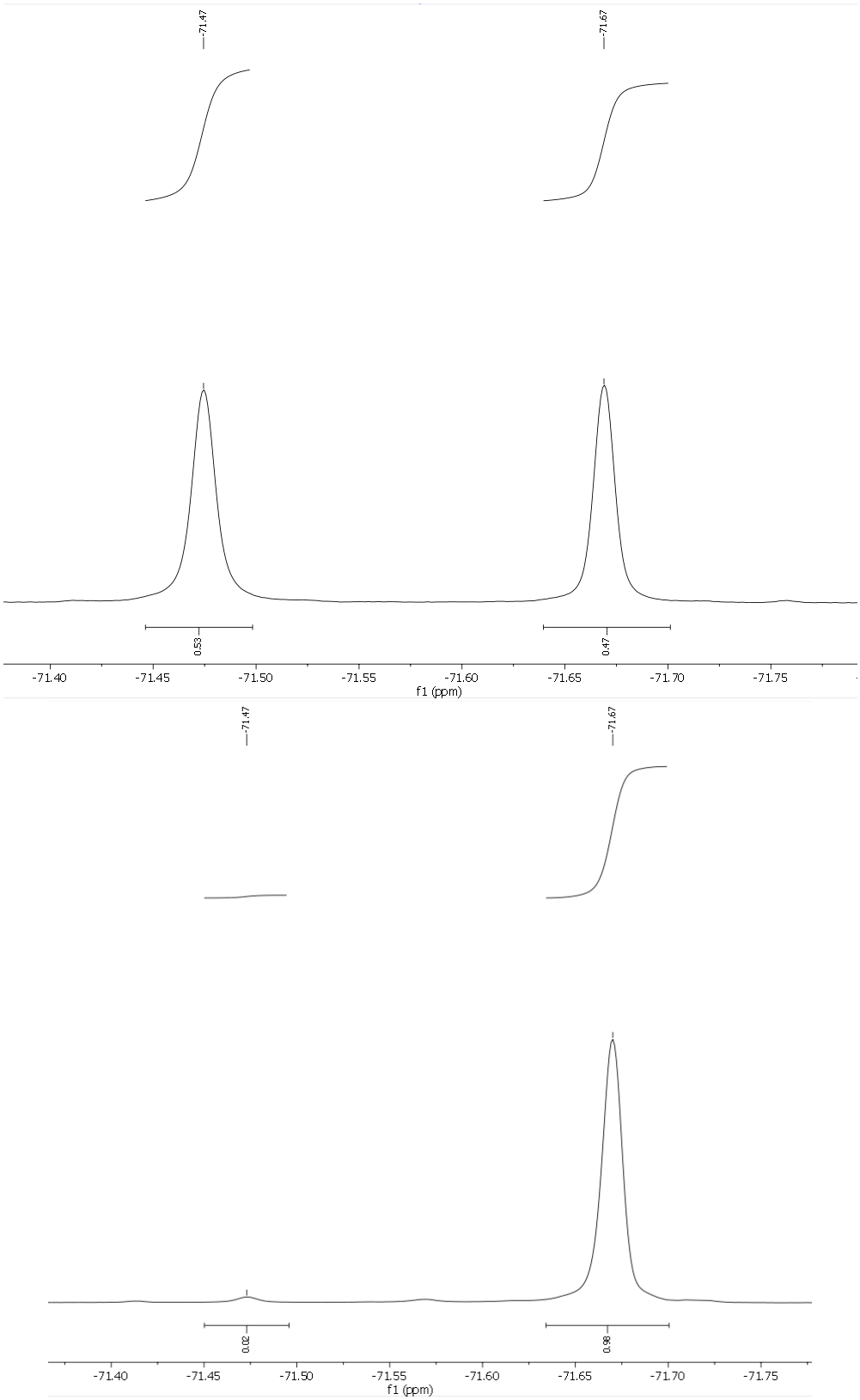
The racemic product was prepared by the same procedure using racemic ligand and isolated only by the preparative TLC.

^1H NMR (400 MHz, $CDCl_3$) *δ* 3.63–3.57 (m, 1H, CH), 3.37 (s, 3H, CH_3), 3.15–3.08 (m, 1H, CH), 2.89 (brs, 1H, OH), 1.92–1.40 (m, 12H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) *δ* 86.54, 74.80, 56.55, 30.36, 26.95, 26.41, 25.88, 24.76, 23.71.

The recorded values were in agreement with the published data.[65]

Figure 36: ^{19}F NMR spectra of Mosher esters of *rac*-**9wc** and (*S,S*)-**9wc**.

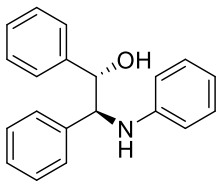


5.4. Ring-Opening of *meso*-Epoxides with Amines

General procedure for ring opening of epoxides: synthesis of 1,2-aminoalcohols (a typical example). The respective oxide **1** (0.3 mmol) and amine **6** (0.3 mmol) were added to a prestirred (10 min) solution of $Sc(OTf)_3$ and ligand (*S*,*S*)-**L6** in dry CH_2Cl_2 (1.2 ml) in a 4 ml vial. Then the reaction mixture was stirred at 25 °C for the appropriate period of time, usually until **1** was fully consumed (disappearance of the respective spot on TLC). Finally, the volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel furnished the desired product.

Racemic mixtures of products were prepared by the same procedure using racemic mixture of Bolm's ligand **L3** and isolated only by preparative TLC.

(1*S*,2*S*)-1,2-diphenyl-2-(phenylamino)ethan-1-ol (7ib)



According to the general procedure with aniline **6b** (28 µL, 0.3 mmol), $Sc(OTf)_3$ (15 mg, 0.03 mmol) and ligand **B6** (13 mg, 0.03 mmol) for 2 days. Column chromatography of the residue on silica gel (hexanes/EtOAc 5/1) furnished 73 mg (84%, 99% ee) of the title compound as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.20 (m, 10H, Ar-H), 7.13–7.06 (m, 2H, Ar-H), 6.72–6.66 (m, 1H, Ar-H), 6.61–6.56 (m, 2H, Ar-H), 4.92 (d, *J* = 6.0 Hz, 1H, CH), 4.56 (d, *J* = 6.0 Hz, 1H, CH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.04, 140.63, 140.09, 129.19, 128.69, 128.37, 128.02, 127.69, 127.47, 126.70, 118.32, 114.52, 78.10, 65.13.

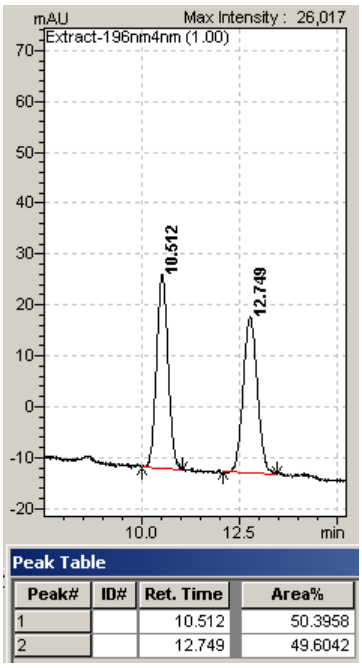
The recorded values were in agreement with the published data.[27]

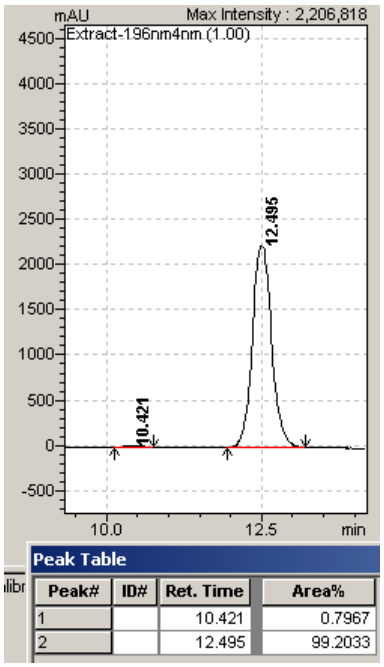
Daicel Chiralpak OD-H, *n*-heptane/IPA 85/15, 1 mL/min, 25 °C, 196 nm,

rac-**7ib**: t_1 = 10.5 min, t_2 = 12.8 min;

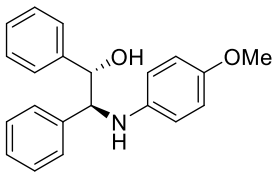
7ib: $t_{S,S}$ = 10.4 min, $t_{R,R}$ = 12.5 min.

Figure 37: HPLC of *rac*-**7ib** and (*S,S*)-**7ib**.





(1*S*,2*S*)-2-((4-methoxyphenyl)amino)-1,2-diphenylethan-1-ol (7ia)



According to the general procedure with 4-methoxyaniline **6a** (37 mg, 0.3 mmol), $Sc(OTf)_3$ (8 mg, 0.015 mmol) and ligand **L6** (7 mg, 0.015 mmol) for 4 days. The reaction furnished the title compound (45% ^{1}H NMR yield, 86% ee). The product was isolated by preparative TLC for HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.14 (m, 10H, Ar-H), 6.69–6.63 (m, 2H, Ar-H), 6.54–6.48 (m, 2H, Ar-H), 4.83 (d, J = 6.5 Hz, 1H, CH), 4.41 (d, J = 6.5 Hz, 1H, CH), 3.67 (s, 3H, OCH_3), 2.76 (s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.68, 152.68, 142.09, 141.43, 140.99, 140.71, 140.44, 140.35, 136.46, 128.63, 128.42, 128.32, 128.24, 127.99, 127.83, 127.62, 127.52, 127.48, 127.15, 126.82, 117.07, 115.92, 115.35, 114.80, 78.26, 66.34, 55.82.

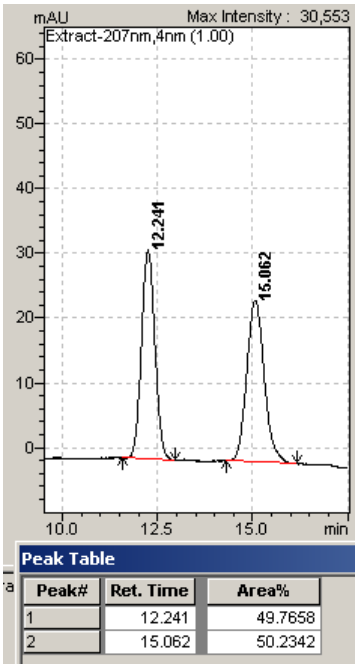
The recorded values were in agreement with the published data.[27]

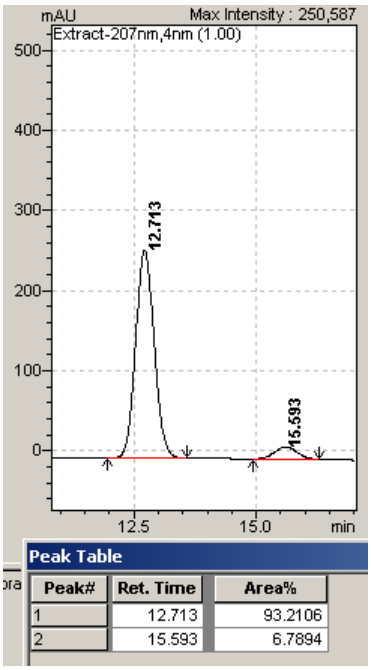
Daicel Chiralpak OD-H, *n*-heptane/IPA 85/15, 1 mL/min, 25 °C, 207 nm,

rac-**7ia**: t_1 = 12.2 min, t_2 = 15.0 min;

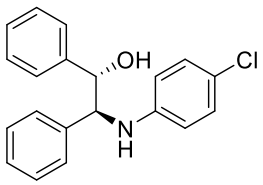
7ib: $t_{S,S}$ = 12.7 min, $t_{R,R}$ = 15.6 min.

Figure 38: HPLC of *rac*-**7ia** and (*S,S*)-**7ia**.





(1*S*,2*S*)-2-((4-chlorophenyl)amino)-1,2-diphenylethan-1-ol (7ic)



According to the general procedure with 4-chloroaniline **6c** (38 mg, 0.3 mmol), $Sc(OTf)_3$ (8 mg, 0.015 mmol) and ligand **L6** (7 mg, 0.015 mmol) for 4 days. The reaction furnished the title compound (53% ^{1}H NMR yield, 97% ee). The product was isolated by preparative TLC for HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.18 (m, 10H, Ar-H), 7.01–6.95 (m, 2H, Ar-H), 6.45–6.38 (m, 2H, Ar-H), 4.89 (d, *J* = 5.4 Hz, 1H, CH), 4.75 (br s, 1H, OH) 4.48 (d, *J* = 5.6 Hz, 1H), 2.34 (br s, 1H, NH).

^{13}C NMR (10j1 MHz, $CDCl_3$) δ 145.98, 140.57, 139.95, 129.00, 128.80, 128.47, 128.16, 127.83, 127.36, 126.60, 122.58, 115.26, 78.08, 64.82.

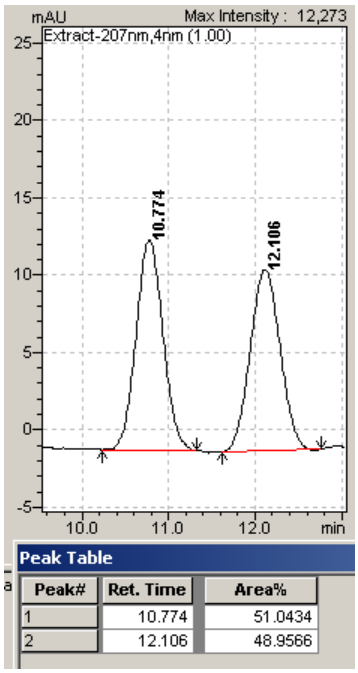
The recorded values were in agreement with the published data.[27]

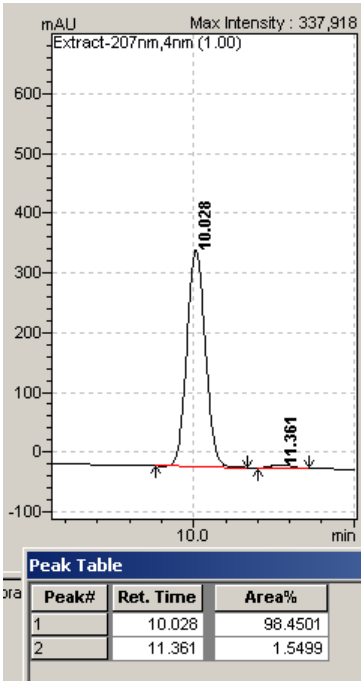
Daicel Chiralpak OD-H, *n*-heptane/IPA 85/15, 1 mL/min, 25 °C, 207 nm,

rac-**7ic**: t_1 = 10.8 min, t_2 = 12.1 min;

7ic: $t_{S,S}$ = 10.0 min, $t_{R,R}$ = 11.4 min.

Figure 39: HPLC of *rac*-**7ic** and (*S,S*)-**7ic**.





6. Conclusion

i. The scope of alcohols in the reaction with *cis*-stilbene oxide catalyzed by Scandium(III) triflate with ligand **L6** was tested. The products were obtained with excellent enantioselectivities up to 99% ee using only 2 mol% load of the catalyst. All variety of substrates such benzyl alcohols substituted with electron withdrawing and donating groups, various aryl and heteroaryl alcohols could be used. Reasonable enantioselectivities were also obtained with aliphatic alcohols. All new compounds were properly characterized.

ii. It was found out that repetitive drying of the same Scandium(III) triflate leads to products in low both yields and enantioselectivities. Therefore, it is necessary to use the catalyst purchased as received, which is then one time dried.

iii. One 2,3-bis(4-chlorophenyl)epoxide was tested in the reaction with 4-methoxy benzyl alcohol which gave rise to the corresponding product with 97% ee.

iv. Aliphatic epoxides were also utilized in the ring-opening reaction using ligand **L6**. Six- and 8-membered cyclic epoxide were tested. Cyclohexene oxide provided product in low 33% ee, but a larger cyclic epoxide, *cis*-cyclooctene oxide, gave rise to a product with higher enantioselectivity of 96% ee. The reaction with *cis*-butene oxide yielded product with 52% ee.

v. Last but not least, the reactions of *cis*-stilbene oxide with different anilines were studied as well. In the reaction with aniline with 10 mol% load of the Sc/**L6** system, the corresponding product was obtained with 99% ee. The product was still formed in good enantioselectivity (87%) by lowering load to 1 mol%. The reaction with 4-chloroaniline provided product with 97% ee, yet with 4-methoxyaniline with just 86% ee using 5 mol% load of the Sc/**L6**. The catalytic systems In/**L6** and Fe/**L6** were also studied in the ring-opening reaction of *cis*-stilbene oxide. Products were formed in good enantioselectivities up to 91% ee.

7. Acknowledgment

I would like to express my gratitude to my supervisor prof. Martin Kotora for allowing me to participate in this project. Additionally, I thankful to him for all support and good advices I have received from him and especially his willingness to patiently explain the obvious.

I want to thank Eva Bednářová, PhD. for her patience and mentorship as I picked up the basics in the laboratory. Without a doubt, I am thankful to everyone else in the Kotora group for a friendly environment. Thanks also to Czech Science Foundation (GAČR) for their financial support.

Likewise, I would like to thank my former teacher Marcel Tkáč, then Marek, Ladislav and others for unveiling me the exhilarating path of chemistry.

I would like to express my deep gratitude to all my family and friends for being so understanding of my partial absence from their lives during much of this process and for their constant efforts to keep me sane. Most importantly I must thank Him, to whom I owe both the beauty of this world I study and the brain to make sense of them, and without whom I would have given up on this project long ago.

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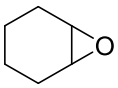
Appendix



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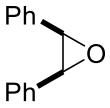

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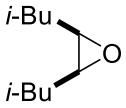

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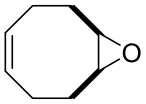

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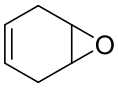

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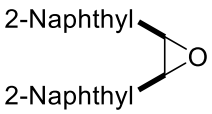

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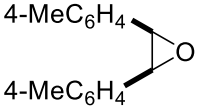

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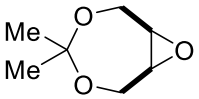

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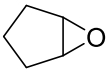

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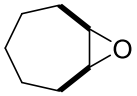

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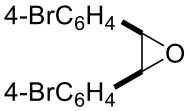

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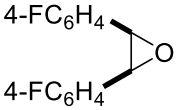

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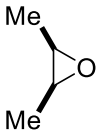

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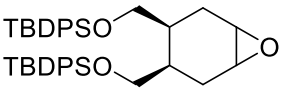

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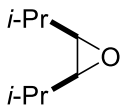

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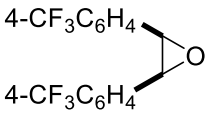

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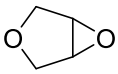

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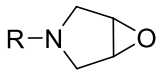

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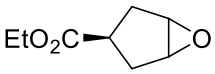

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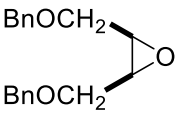

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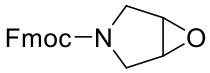

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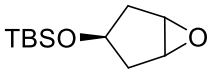

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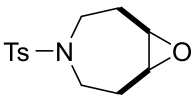

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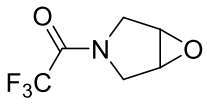

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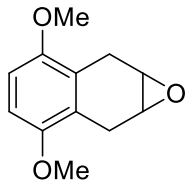

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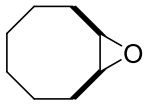

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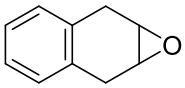

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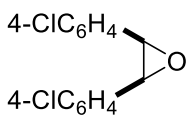

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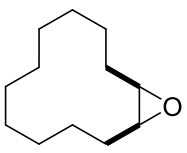

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